Pharmacokinetics of meropenem in critically ill patients with varying renal function

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Background and Objectives

Meropenem (MER) is a carbapenem antibiotic frequently used to treat severe infections in critically ill patients, e.g. caused by *Pseudomonas aeruginosa* [1]. In these patients, an early initiation of appropriate antibiotic therapy is crucial [2]. MER is primarily excreted renally and its activity has been shown to correlate with the time during which drug concentrations are above the minimal inhibitory concentration ($T_{>MIC}$) [3]. The objective of the present work was to evaluate standard dosing of MER in critically ill patients with varying renal function with respect to pharmacokinetic/pharmacodynamic (PK/PD) target attainment.

Methods

Study design

- A prospective, single centre, observational study was conducted at the University Hospital of Munich in critically ill patients with severe infections. In the present analysis, 41 patients without renal replacement therapy were included (Tab.1).
- All patients received standard doses of MER (1000 mg: n=40; 1000 mg/ 2000 mg: n=1) every 8 hours as 30 min intravenous infusion (Fig.1).
- Rich serum sampling was performed over 4 days (n_{median}=33/patient; Fig. 1, 2) and total MER concentrations were quantified by liquid chromatography tandem mass spectrometry [4].

Table 1: Summary of patient characteristics at the first study day.

Continuous patient characteristics	**Median (range)**	**5th - 95th percentiles**
Age [years]	56.0 (25.0-84.0)	32.0-70.0
Weight [kg]	70.0 (44.0-140)	47.0-121
BMI [kg/m²]	23.0 (16.0-49.0)	18.0-40.0
APACHE II Score [-]	27.0 (13.0-38.0)	14.0-36.0
SOFA Score [-]	11.0 (2.00-17.0)	4.00-15.0
$CLCR_{UC}$* [mL/min]	82 (19.0-229)	19.9-174
$CLCR_{CG}$ [mL/min]	80.8 (24.8-191)	39.4-170
IL-6 [pg/mL]	88.3 (9.90-10096)	24.0-1460
CRP [mg/dL]	8.90 (2.00-34.6)	2.10-32.0
Categorical patient characteristics	**Percentage of patients**	
Sex (male)	58.5	-
Sepsis	82.9	-
Transplantation**	58.5	-
ECMO	4.88	-

BMI: Body mass index; $CLCR_{UC}$: Creatinine clearance measured with urine collection method; $CLCR_{CG}$: Creatinine clearance estimated according to Cockcroft Gault; *IL-6*: Interleukin 6; *CRP*: C-reactive protein; *ECMO*: Extracorporeal membrane oxygenation; *$n_{missing}$=3; **Liver or lung transplantation within the last 28 days.

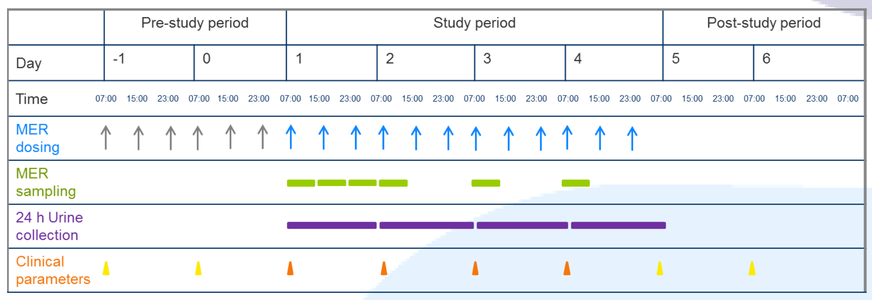

Figure 1: Schedule of study design. *Grey arrows*: MER dosing before start of the study; *blue arrows*: MER dosing within the study period; *green bars*: sampling intervals; *purple bars*: 24 hours urine collection interval; *orange, yellow triangles*: clinical parameter measurements.

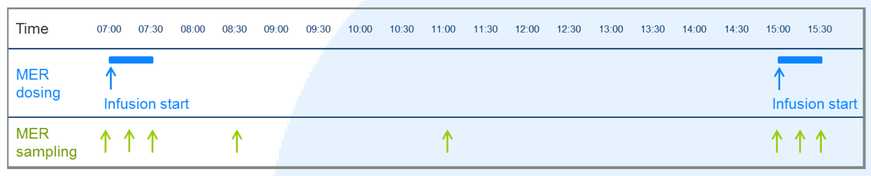

Figure 2: Sampling schedule in detail. *Blue arrows*: start of the infusion; *green arrows:* sampling time points (15 min, 30 min, 1.5 h, 4 h, 8 h (directly before next dose) after start of the infusion).

Population pharmacokinetic modelling & PK/PD simulations

- Modelling and simulation activities were performed using NONMEM 7.3 (FOCE+I [5]); statistical and graphical data analyses were conducted in R 3.2.2 [6]. During covariate analysis, longitudinally measured continuous covariates were linearly interpolated.
- The model was used to simulate 1000 PK profiles for varying creatinine clearance (CLCR) values (30-170 mL/min) for the first day of treatment. The probability to attain 40%$T_{>MIC}$ (=bactericidal target) was calculated for the MIC range of *Pseudomonas aeruginosa* (0.008-256 mg/L; due to negligible protein binding of MER, total concentrations were used) [3,7]. A probability of target attainment of ≥90% was considered sufficient treatment.

Results (I)

Population pharmacokinetic modelling

- A two-compartment model with linear elimination adequately described MER PK in the critically ill population (Tab. 2, Fig. 3-5). Highest interindividual variability (IIV) was observed for CL, followed by V_1 and V_2 (Tab. 2).
- CLCR estimated according to Gockcroft Gault ($CLCR_{CG}$; implemented as a linear function) was found to be a statistically significant and clinically relevant covariate on CL, explaining ~50% of IIV on CL (Tab. 2).

Table 2: Parameter estimates of the population PK model.

Parameter	**Estimate (RSE, %)**	
	Base model	Population PK model
OFV	4913.332	-266.508 4646.824
θ CL [L/h]	8.82 (8.00)	9.11 (4.00)
θ V_1 [L]	8.41 (13.2)	8.19 (12.3)
θ Q [L/h]	30.9 (16.8)	30.6 (14.9)
θ V_2 [L]	17.8 (8.00)	17.0 (6.90)
θ $CLCR_{CG}$_CL, %	-	0.935 (9.00)
ω CL, %CV	55.0 (9.00)	28.3 (16.9)
ω V_1, %CV	41.5 (13.7)	43.0 (12.7)
ω V_2, %CV	21.6 (14.0)	21.0 (13.7)
σ proportional, %CV	24.1 (7.40)	21.1 (6.80)
σ additive [mg/L]	0.367 (28.3)	0.455 (28.7)

Relative standard errors (RSE) of the random effect parameters are reported on standard deviation scale; IIV was implemented assuming a log-normal distribution of the individual PK parameters; *CL*: clearance for a patient with a $CLCR_{CG}$ of 80.8 mL/min; *$CLCR_{CG}$_CL*: fractional change of CL per mL/min deviation from the $CLCR_{CG}$ 80.8 mL/min.

Results (II)

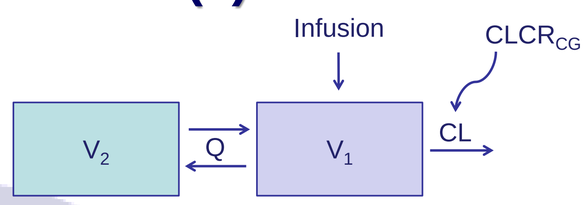

Figure 3: Schematic illustration of the population PK model. V_1: Central volume of distribution; V_2: Peripheral volume of distribution; *Q*: Intercompartmental clearance; *CL*: Clearance; $CLCR_{CG}$: Creatinine clearance estimated according to Cockcroft Gault.

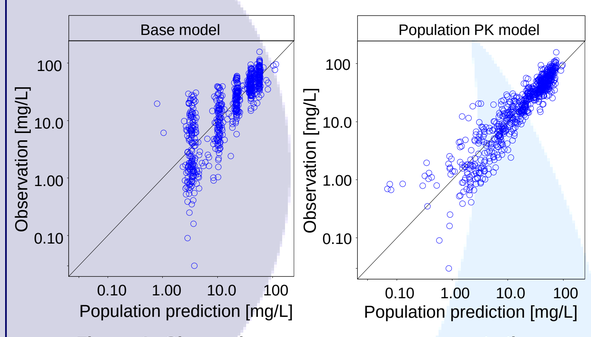

Figure 4: Observed meropenem serum concentration vs. population predicted meropenem serum concentration. *Left*: Basemodel, *right*: population PK model.

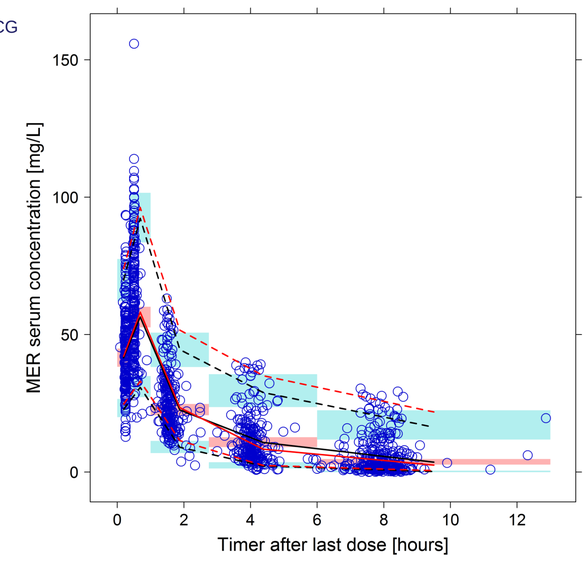

Figure 5: Visual predictive check of the population PK model (n=1000). *Blue circles*: observations, *Lines*: 5th, 95th percentile (dashed), 50th percentile (solid) of the observed (red) and simulated (black) data. *Shaded areas*: 95% confidence interval around simulated percentiles.

Stochastic PK/PD simulations

- For susceptible *P. aeruginosa* isolates (MIC ≤2 mg/L), the PK/PD target would be attained for all patients, independent of their renal function (Fig. 6, 7).
- If infected with isolates with MIC 8 mg/L (intermediate/resistant EUCAST breakpoint), only patients with severe or moderate renal insufficiency would reliably reach the target (Fig. 6, 7).
- For resistant isolates with MIC 16 mg/L, only patients with severe renal insufficiency would attain the target. For resistant isolates with MIC >16 mg/L, none of the investigated patients would be treated adequately (Fig. 6, 7).

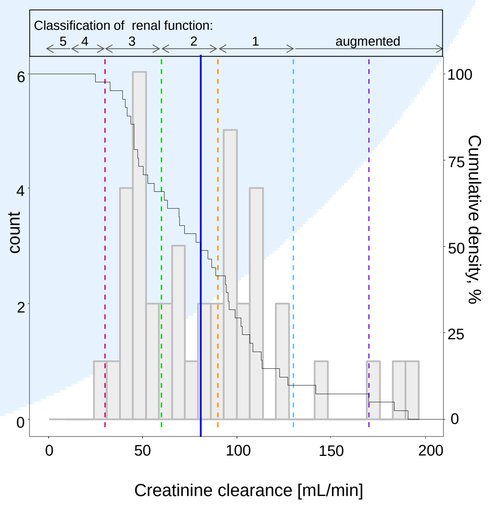

Figure 6: Frequency distribution of creatinine clearance at first study day. *Black curve*: cumulative density; *blue solid line:* median; *purple dashed line*: 95th percentile; *pink, green, orange and light blue dashed lines*: separate CLCR into renal function classes [8] (Glomerular filtration rate (GFR) <15 mL/min: end stage renal disease, GFR 15-29 mL/min: severe renal insufficiency, GFR 30-59 mL/min: moderate renal insufficiency, GFR 60-89 mL/min: mild renal insufficiency, GFR 90-130 mL/min: normal renal function, GFR >130 mL/min: augmented renal function).

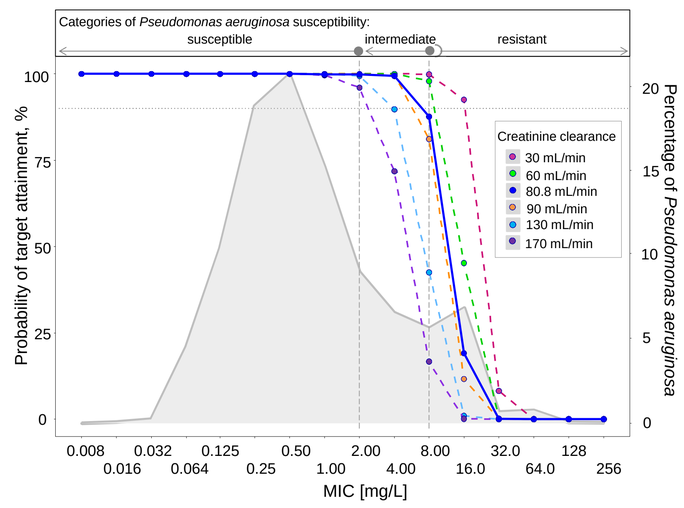

Figure 7: Probability to attain the PK/PD target 40%$T_{>MIC}$ for the MIC distribution of *Pseudomonas aeruginosa for* varying renal function at first day of treatment. *Dashed vertical lines*: EUCAST MIC breakpoints [7] (susceptible/intermediate: 2 mg/L, intermediate/resistant: 8 mg/L); *Dotted horizontal line:* PTA of 90%; *Shaded grey area*: MIC distribution of *P. aeruginosa* [7]; *Curves:* PTA for varying renal function (*blue solid:* median, *purple dashed:* 95th percentile, *pink dashed:* 30 mL/min, *green dashed:* 60 mL/min, *orange dashed:* 90 mL/min, *light blue dashed:* 130 mL/min).

Discussion and Conclusions

- A population PK model was successfully developed to describe the PK of MER in a critically ill population. The highest interindividual variability was found on clearance, whereof ~50% was explained by the covariate renal function.
- Standard dosing of MER resulted in adequate MER serum concentration-time profiles on the first day of treatment if infected with susceptible *Pseudomonas aeruginosa* isolates. For intermediate isolates, dose adjustment seems to be required dependent on the renal function of the patient.
- As a next step, additional covariates will be analysed to further explain the high PK variability in this vulnerable patient population.

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