

Use of Monte Carlo Simulation to Determine Optimal Meropenem Regimens in Patients Receiving SHIFT Renal Replacement Therapy

Introduction

- Current antibiotic dosing regimens often result in subtherapeutic concentrations in critically ill patients, but limited pharmacokinetic (PK) data exist to optimize antibiotic dosing. [1]
- Monte Carlo simulations with mathematical PK modeling based on literature based data can be applied to determine the optimal antibiotic dosing regimens to treat critically ill patients receiving renal replacement therapy (RRT).
- Meropenem is currently recommended as empiric treatment in critically ill patients, but no PK data are available for SHIFT RRT, a daily prolonged RRT, used as an alternative to CRRT.

Objective

To conduct "in silico" PK trials to determine initial meropenem dosing recommendations in critically ill patients receiving SHIFT RRT.

Methods

Mathematical PK Model Development

- One compartment model with the first elimination order was used to generate free meropenem serum concentrations for 48 hours of initial therapy.
- Demographic and PK parameters with their associated variability derived from relevant previous PK studies were incorporated into the models.

Methods

Table 1. Input Parameters Used in In-Silico PK Trials [2-15]

SHIFT Regimens	Parameters	Hemofiltration (HF)		Hemodialysis (HD)	
		300 mL/min	300 mL/min	300 mL/min	300 mL/min
SHIFT Regimens	Qblood	5 L/h	4 L/h	5 L/h	4 L/h
	Qeffluent	8 h	10 h	8 h	10 h
	Duration	Daily	Daily	Daily	Daily
	Frequency	Daily	Daily	Daily	Daily
Demographic & Pharmacokinetic Parameters	Weight	86.6±29.2 kg [≥40 kg]			
	Volume of Distribution	0.41±0.18 L/kg [0.08-1.07 L/kg]			
	Unbound Fraction	0.79±0.09 [0-1]			
	Non-renal CL	54.9±49 mL/min [0-251 mL/min]			
	SC or SA	0.84±0.17 [0-1]		0.6±0.12 [0-1]	

- Four different SHIFT RRT regimens were modelled to be instituted either at the beginning of (early SHIFT) or 14-16 hours after meropenem administration (late SHIFT) to ensure a broad range of clinical scenarios and to assess the effect of time of SHIFT in relation to meropenem dose.
- Range limits for and correlation between input parameters were identified from the data and were integrated into the models to construct a virtual cohort with realistic PK parameters.
- SHIFT clearance data were determined from a regression analysis of published meropenem RRT studies. SHIFT clearance in HF was corrected to account for the pre-dilution effect of replacement fluid.

Monte Carlo Simulation

- Monte Carlo simulation was performed in 5,000 virtual patients for each of 10 meropenem dosing regimens.
- Demographic/PK parameters were simulated as log-Gaussian distributions.

Prediction of Probability of Target Attainment (PTA)

- The PTA was determined based on the fraction of virtual patients attaining >40% free meropenem concentration above 4 times minimum inhibitory concentration (MIC) of *Pseudomonas aeruginosa* (2 µg/mL) during the first 48 hours of therapy (40% fT ≥ 4x MIC).
- Optimal regimens were defined as the ones attaining with PTA ≥ 90% in 5,000 virtual subjects using the smallest daily dose to minimize the risk of drug toxicity.

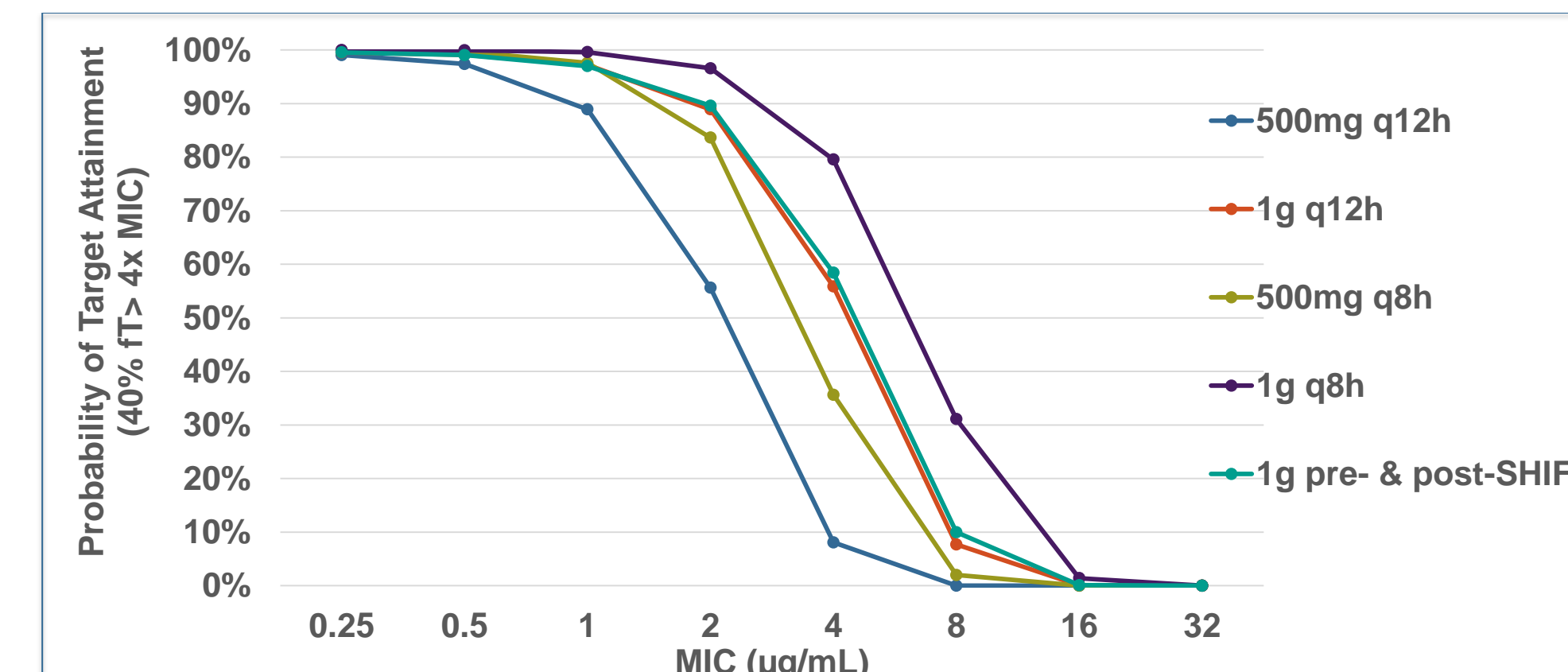
Results

- Meropenem 1g q12h and 1g pre & post SHIFT were optimal dosing regimens in all SHIFT regimens. The PTA difference of these optimal regimens in early or late SHIFT was all within 1-2%.
- Weight-based dosing or pre & post SHIFT dosing did not result in better PTA than standard dosing regimens.
- Mean meropenem clearance and half-life was 5.9±2.5 L/h and 4.9±3.4 h during SHIFT, and 3.1 ± 2.4 L/h and 14.2±16.7 h off-SHIFT, respectively.

Table 2. PTA and the Proportion of fT≥4xMIC in 5000 Virtual Subjects Receiving Different Meropenem Regimens

Dosing	Early SHIFT RRT		Late SHIFT RRT	
	%PTA (>40% fT>4xMIC)	%fT>4xMIC (mean±SD)	%PTA (>40% fT>4xMIC)	%fT>4xMIC (mean±SD)
1g q24h	0.26	0.34 ± 0.22	0.67	0.56 ± 0.26
500mg q12h	0.56	0.46 ± 0.25	0.63	0.52 ± 0.29
1g q12h	0.90	0.75 ± 0.22	0.92	0.81 ± 0.23
2g q12h	0.97	0.89 ± 0.18	0.98	0.92 ± 0.16
5.8mg/kg q12h	0.54	0.46 ± 0.26	0.63	0.53 ± 0.29
11.6mg/kg q12h	0.87	0.74 ± 0.24	0.90	0.80 ± 0.24
500mg q8h	0.84	0.69 ± 0.24	0.84	0.72 ± 0.27
1g q8h	0.97	0.88 ± 0.17	0.97	0.91 ± 0.17
500mg pre & post SHIFT	0.59	0.50 ± 0.29	0.54	0.47 ± 0.29
1g pre & post SHIFT	0.90	0.79 ± 0.24	0.89	0.78 ± 0.25

Figure. PTA of Selected Meropenem Regimens at Different MICs



*Figure illustrates 8h HD & early SHIFT but is illustrative of all modelled SHIFT settings.

Conclusion

- Monte Carlo simulations with literature-based relevant demographic and PK data can be a powerful tool to predict the optimal antibiotic dosing in critically ill patients receiving SHIFT RRT.
- Our simulation study suggests that daily 8 or 10 hour SHIFT RRT will clear meropenem substantially.
- Meropenem 1g q12h is recommended to attain pharmacodynamic target in critically ill patients receiving daily 8 or 10 hour SHIFT RRT and agrees with those published recommendations for other hybrid RRTs. [12,16]
- Future clinical studies are warranted to validate these findings.

References

- Seyler L, et al. *Crit Care*. 2011; 15(3):R137.
- Gashti CN, et al. *Am J Kidney Dis*. 2008;51(5):804-810.
- Leroy A et al. *Eur J Clin Pharmacol*. 1992;42(5):535-538.
- Christensson BA, et al. *Antimicrob. Agents Chemother*. 1992;36(7):1532-1537
- Thalhammer F, et al. *Antimicrob. Agents Chemother*. 1988;42(9):2417-2420.
- Krueger WA, et al. *Antimicrob. Agents Chemother*. 1998;42(9):2421-2424.
- Meyer MM, et al. *Am J Kidney Dis*. 1999;33(4):790-795.
- Giles LJ et al. *Crit Care Med*. 2000;28(3):632-637.
- Ververs TF, et al. *Crit Care Med*. 2000;28(10):3412-3416.
- Robatel C et al. *J Clin Pharmacol*. 2003;43(12):1329-1340.
- Isla A, et al. *J Clin Pharmacol*. 2005;45(11):1294-1304.
- Kielstein JT, et al. *Crit Care Med*. 2006;34(1):51-56.
- Langgartner J, et al. *Intensive Care Med*. 2008;34(6):1091-1096.
- Bilgrami I et al. *Antimicrob. Agents Chemother*. 2010;54(7):2974-2978.
- Afshartou D, et al. *Am J Kidney Dis*. 2014;63(1):170-171.
- Deshpande P, et al. *Nephrol Dial Transplant*. 2010;25(8):2632-2636.

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