Meropenem Dosing Recommendations For Thai Critically Ill Patients Receiving Continuous Renal Replacement Therapy

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Introduction

- Antibiotic dosing in critically ill patients undergoing continuous renal replacement therapy (CRRT) is still a challenge.
- Meropenem is one of the most common antibiotics used in intensive care unit. It could be removed by CRRT due to its pharmacokinetics (PK) of low volume of distribution, small molecular weight and low protein binding affinity. [1]
- Current antibiotic dosing regimens often result in subtherapeutic concentrations in critically ill patients receiving CRRT. [2]
- Unfortunately, recommendations of meropenem dosing regimens mostly are suggested from published PK studies of the Western literatures. Differences in PK of various populations such as body weights and non-renal clearance may contribute to the need for dosing adaptation.
- Monte Carlo Simulation (MCS) can be an effective tool to predict the optimal antibiotic dosing regimens to treat infectious diseases in critically ill patients receiving RRT. [3]

Objective

To develop optimal dosing recommendations of meropenem for Gram negative infections in Thai critically ill patients receiving CRRT via MCS with pharmacokinetic and pharmacodynamic models.

Method

Mathematical pharmacokinetic model development

- Demographic and PK parameters and associated variability from previously published meropenem studies in Thai critically ill patients were gathered to develop models for virtual patients receiving CRRT. [Table 1]
- Body weight used in the models was extracted from *Srisawat and colleagues* to represent body weights of Asian population. [4]
- A one compartment PK model with first order elimination and 2 CRRT settings with 3 different effluent rates of 20, 25 and 35 mL/kg/hour was created to predict meropenem deposition for 48 hours of initial therapy.
- Range limits and correlation on input parameters estimated from the data were included in the models to construct a virtual cohort with population-specific pharmacokinetic parameters.

Table 1. Input parameters used in Mote Carlo simulation trials. [4-9]

		Hemofiltration (HF)	Hemodialysis (HD)
Pharmacokinetic parameters Mean±SD (range limits)	Weight (kg)	60.83±16.25 (40-98.1)	
	V_d (L/kg)	0.23±0.18 [0.12-0.84]	
	CL_{NR} (mL/min)	56.5±59.83 mL/min [12.3-194.8]	
	Free fraction	0.79±0.09(0.63-0.98)	
	SC or SA	0.965±0.179 (0.21-1)	0.85±0.230 (0.35-1)

Monte Carlo simulation

- The dosing regimens including the recommended doses from published resources for critically ill patients receiving CRRT and patients with normal renal function were simulated.
- MCS was performed to generate drug concentration profiles for each regimen in a different group of 5,000 virtual patients.

Prediction of probability of target attainment (PTA)

- Meropenem regimens were evaluated on the probability of attaining percent of duration of free drug concentrations to the 4 times minimum inhibitory concentration (MIC) of *Pseudomonas aeruginosa* (2 µg/mL) of > 40% for the initial 48 hours-therapy. [10]
- The optimal regimen was defined as occurring when ≥ 90% of virtual patient attained the target attainment with the lowest daily dose to minimize the toxicity risk.

Results

- A meropenem dosing regimen of 750 mg every 8 hours achieved a PTA > 90% with smallest total daily dose in all three modalities with KDIGO recommended effluent rates of 20-25 mL/kg/hr.
- PTAs of meropenem regimens from available clinical resources were presented in Table 2.
- Figure 1 illustrated the PTA results of the modality with an effluent rate of 25 mL/kg/hour, different meropenem regimens, various MICs.
- As an increasing effluent rate of 35 ml/kg/hour that might be performed in some clinical settings, the same regimen of 750 mg every 8 hours attained the pharmacodynamic target. (Table 3)

References

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Results (continued)

Table 2. Average daily PTAs over 48 hours in each 5000 virtual patients receiving 25 and 35 mL/kg/hour continuous venovenous hemofiltration with selected meropenem regimens from clinical resources.

Selected Dosing Regimens	PTA (Average %FT/MIC)	
	Effluent rates	
	25 mL/kg/hour	35 mL/kg/hour
500 mg q 12 h	0.559	0.4776
750 mg q 12 h	0.7628	0.7144
1000 mg LD 500 mg q 12 h	0.6624	0.5910
1000 mg q 12 h*	0.8458	0.8132
1500 mg q 12 h*	0.9166	0.8954
2000 mg q 12 h	0.9462	0.9286
500 mg q 8 h*	0.8198	0.7932
750 mg q 8 h*	0.9320	0.9162
1000 mg LD 500 mg q 8 h*	0.8600	0.8342
1000 mg q 8 h*	0.9662	0.9636
2000 mg q 8 h	0.9938	0.9924

*Recommended meropenem dosing regimens for patients receiving CRRT from available clincial resources

Figure 1 The PTA result of 25 mL/kg/hour continuous venovenous hemodifiltration modality with selected meropenem regimens from available clinical resources.

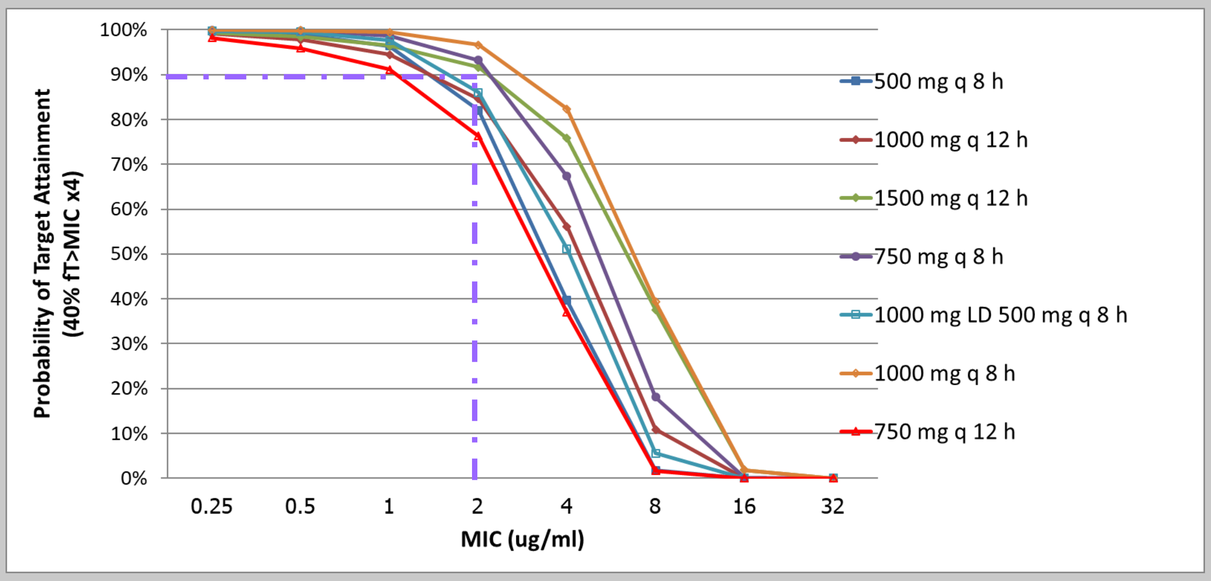

Table 3. Optimal meropenem dosing regimens for Thai critically ill patients receiving continuous renal replacement therapy with different effluent flow rates and modalities*

Effluent flow rates/Modalities	CVVH	CVVHD
20 mL/kg/hour	750 mg every 8 hours	
25 mL/kg/hour		
35 mL/kg/hour		

*Optimal dose of meropenem for a %fT/4MIC of ≥ 40 % with MIC of 2 µg/mL for meropenem, at different effluent rates and CRRT modalities.

Discussion/Conclusion

- This is the first study using MCS to identify the optimal doses of meropenem for *Pseudomonas aeruginosa* infections in Thai critically ill patients receiving CRRT.
- MCS with literature-based demographic and PK data from critically ill patients can be a powerful tool to predict the drug concentration profiles and antibiotic dosing in critically ill patients receiving CRRT.
- Meropenem dosing regimen of 750 mg every 8 hours are suggested in these Thai critically ill patients receiving CRRT.
- Some meropenem dosing regimens from available clinical resources could not attain the PTA target that may contribute to therapeutic failure.
- Application of our dosing recommendation should be limited to critically ill patients receiving CRRT with similar parameters as the virtual patients.
- Clinical validation of these recommendations is required.