Meropenem Dosing Recommendations in Critically Ill Patients Receiving Prolonged Intermittent Renal Replacement Therapy

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Introduction

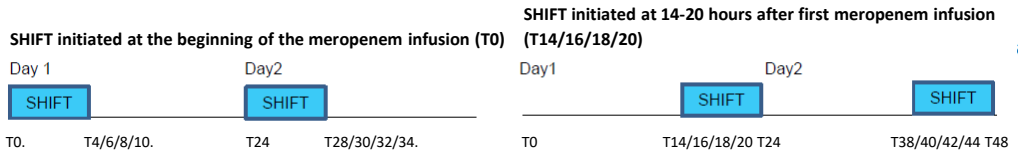
- Prolonged intermittent renal replacement therapy (PIRRT) is a daily 8-10 hour renal replacement therapy (RRT) for treating acute kidney injury in critically ill patients. Moreover, PIRRT duration has been modified into 4-6 hours in some institutes. [1]
- Meropenem is a carbapenem antibiotic that has been used for managing critically ill patients with severe infections. [2]
- Meropenem can be removed via PIRRT due to its pharmacokinetics (PK). [2]
- Unfortunately, PK studies of meropenem in patients undergoing PIRRT therapy are limited. There is no standard meropenem dosing recommendation that existed for these patients.
- Our study aimed to evaluate the probability of target attainment (PTA) of various meropenem regimens in critically ill patients receiving PIRRT utilizing Monte Carlo simulation (MCS)

Methods and Materials

Mathematical PK Model Development

- Mathematical models with first order elimination were created using published demographic and pharmacokinetics in adult critically ill patients. [Table 1]
- Different daily PIRRT with dialysis technique and effluent rate of 18L/h with various PIRRT duration of 4, 6, 8, 10 h were performed in the models.
- Early and late PIRRT occurred at the beginning of and 14-20 h after drug administration were simulated. [Figure 1]
- Range limits and correlation on input parameters estimated from the data were included in the models to construct a realistic virtual population.

Fig 1 Clinical scenarios of PIRRT modalities



Monte Carlo Simulation

- MCS predicted drug disposition during the first 48 h in 10,000 virtual patients for each drug regimen.
- All recommended doses from published resources for critically ill patients receiving CRRT, intermittent hemodialysis and patients with normal renal function were simulated

Prediction of Probability of Target Attainment (PTA)

- Desired pharmacodynamic target to calculate PTA was 40% of free drug concentration that exceeds 4 times of the MIC of 2 mg/L. [3,4]
- The optimal dosing regimens were defined as the ones reached 90% of PTA in all PIRRT settings.

Table 1 Input Parameters Used in Monte Carlo Simulation Trials [5-12]

		Hemodialysis
Daily PIRRT Settings	$Q_{effluent}$	18 L/h
	Q_{blood}	12 L/h
	Duration	4, 6, 8, 10 hours
	Frequency	Daily
PK Parameters Mean±SD (range limits)	Weight (kg)	86.6±29.2 (40-∞)
	V_d (L/kg)	0.42 ± 0.19 (0.08-1.07)
	CL_{NR} (mL/min)	3.29 ± 2.42 L/h (0-15.09)
	Saturation coefficient (SA)	0.77 ± 0.31 (0.15-1.13)

Results

- All recommended meropenem dosing regimens including the clinical resources were evaluated for PTA in our models. (Table 2 and Figure 2 shown the PTA results of late 8-hour PIRRRT as a representative modality)
- Interestingly, some dosing suggestions achieved less than 90% of the PTA target.
- For early PIRRT with duration less than or equal 6 h, the regimen of 500 mg q 8 h with supplemental dose of 500 mg after PIRRT is recommended while PIRRT duration of more than 6 h requires a dose of 750 mg q 12 h with a supplemental dose of 500-750 mg after PIRRT.
- Additionally, the dosing regimen of 1000 mg loading dose, then 500 mg q 8 h is recommended for late PIRRT duration less than or equal 6 h.
- For late PIRRT of 8 and 10 h, the recommended doses should be 1000 mg q 12 h and 750 mg q 8 h, respectively.

Table 2 PTAs in 10,000 Virtual Patients Receiving 6-hour PIRRT hemodialysis with Different Meropenem Regimens

Dosing	Early PIRRT	Late PIRRT
	PTA (%) (40% fT>MIC)	
1000 mg LD, 500 mg q 8 h	78.42	***88.77***
1000 mg q 8 h	96.83	98.07
750 mg q 8 h	92.75	94.6
500 mg q 8 h	73.28	78.92
1000 mg q 12 h (literature-based recommendation)	80.99	93.33
Dosing with supplemental doses (SD) in Early PIRRT		
1000 mg LD, 500 mg q 8 h with 500 SD	94.10	
1000 mg q 8 h with 1000 SD	99.46	
750 mg q 8 h with 750 SD	98.49	
500 mg q 8 h with 500 SD	***91.87***	
1000 mg q 12 h with 1000 SD	97.58	

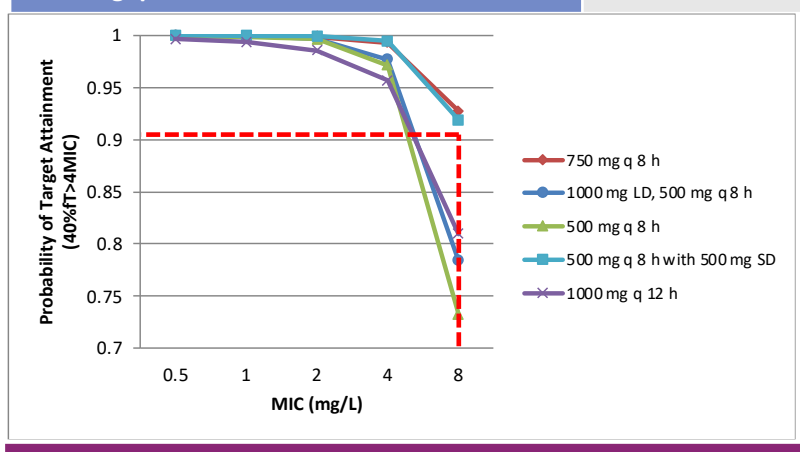


Figure 2 PTA of Selected Meropenem Regimens at Different MICs in patients receiving 6-hour Early PIRRT therapy with hemodialysis modality

Discussion/Conclusions

- This is the first study using Monte Carlo Simulation to identify the optimal dose of meropenem for Gram negative infections in critically ill patients receiving various PIRRT durations.
- Previous recommended meropenem dosing regimens could not attain the PTA target.
- The dosing regimens should be considered based on PIRRT characteristics such as duration of treatment and time to commence PIRRT.
- For early PIRRT, dosing regimens with supplemental doses showed highest PTA with lowest daily doses.
- Clinical validation is needed to confirm the results of our study.

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Acknowledgement

This research project is supported by grants for development of new faculty staff, Ratchadaphiseksomphot Fund, Chulalongkorn University