Monte Carlo Simulation to Determine Meropenem Dosing in Critically ill Patients Receiving Five Kidney Replacement Therapy Regimens

Susan J. Lewis, PharmD, BCPS[1]; Bruce A. Mueller, PharmD, FCCP, FASN, FNKF[2]
[1]College of Pharmacy, University of Findlay, [2]College of Pharmacy, University of Michigan

Abstract

Introduction: The Tablo Hemodialysis System (Tablo) offers a range of kidney replacement therapy (KRT)options for critically ill patients requiring dialysis. The use of the wide variety of dialysate flow rates and treatment regimens available may clear drugs like meropenem differently than conventional devices. The purpose of this Monte Carlo Simulation (MCS) was to develop meropenem doses likely to attain therapeutic targets for a variety of dialysis prescriptions on Tablo.
Methods: One compartment, first-order pharmacokinetic models were built using relevant demographic information and pharmacokinetic variables to generate free meropenem plasma concentration over a week in 5,000 virtual anuric patients receiving 5 different KRTs. MCS was performed to assess the probability of target attainment (PTA) for various meropenem doses with 0.5-hour infusions (Table 1). The 2 pharmacodynamic targets were ≥40% free plasma concentrations above one time or four times the minimum inhibitory concentration [>40% fT>MIC or >40% fT>4xMIC] assuming Pseudomonas aeruginosa infection with the breakpoint MIC of 2 mg/L. Potential risk of neurotoxicity was also evaluated using the proposed toxicity threshold of total trough concentration of >64 mg/L. Optimal doses were the smallest doses attaining PTA≥90% during 1-week of therapy.
Results: Meropenem doses attaining the desired pharmacodynamic (PD) targets in different Tablo settings are shown in the table. None of the optimal meropenem doses yielded "toxic" trough concentrations.
Conclusions: MCS models suggest that different Tablo KRT regimens require different meropenem dosing strategies. Meropenem doses for sequential therapy were the same as daily HD regimens. More aggressive PD targets require higher doses to attain PTA, but do not appear to achieve concentrations associated with toxicity. These findings need clinical validation.

Introduction

The Tablo Hemodialysis System (Tablo) offers a range of kidney replacement therapy (KRT) options for critically ill patients with AKI. The use of the wide variety of dialysate flow rate and treatment duration & frequencies that are available may clear drugs like meropenem differently than conventional devices. Clinicians need antibiotic dosing recommendations for these new KRT flow rates to ensure that efficacious, non-toxic treatment can be given. Monte Carlo Simulation (MCS) can be used in the absence of clinical pharmacokinetic trials to develop dosing schemes. The purpose of this MCS was to develop meropenem doses likely to attain therapeutic targets for a variety of KRT treatment combinations on Tablo.

Methods and Materials

- One compartment, 1st-order PK models were developed using demographics from a large KRT trial (Bagshaw 2020) & published meropenem PK parameters to predict one week of meropenem exposure in 5,000 virtual patients (>40 kg & anuric) receiving 5 different KRT regimens.
- Meropenem extraction coefficients [EC: SA or SC] were determined from all published cefepime studies using KRT. Meropenem transmembrane clearance (CL) from Tablo KRT was estimated using EC and effluent flow rates [Qeff: Qd or Quf] as follows: CL = EC x Qeff.
- Two efficacy targets were used: 1) ≥40% free plasma concentrations above the minimum inhibitory concentration [>40% fT>MIC] or 2) a more aggressive target of ≥40% free plasma concentrations above four times the MIC >40% [fT>4xMIC], assuming *Pseudomonas aeruginosa* infection with the breakpoint MIC of 2 mg/L.
- The smallest doses attaining targets in ≥90% of subjects during 1-week of therapy were considered optimal.
- Potential risk of neurotoxicity was evaluated using the proposed toxicity threshold of total trough concentration of >64 mg/L.

Body Weight and Pharmacokinetic Parameters Used

Body weight (kg)	88 ± 26 [40-177]
Vd(L/kg)	0.39 ± 0.18 [0.08-1.07]
Non-renal CL (mL/min)	38.3 ± 25.6 [0-104.8]
Unbound fraction of drug	0.98 ± 0.16 [0-1]
Extraction coefficient	Qd 300 ml/min : SA = 0.37 ± 0.07 [0-1] Qd 100 ml/min: SA= 0.65 ± 0.13 [0-1] Qd 50 ml/min: SA = 0.83 ± 0.16 [0-1] Quf 5 ml/min: SC = 0.98 ± 0.2 [0-1]

Sample Model 3 (Sequential Therapy) Results

Probability of Target Attainment (PTA) in 5000 Virtual Patients with Each Meropenem Dosing Regimen

Meropenem Dosing Regimen	MIC (mg/L)	PTA (%) of 1-week		PTA (%) of Each Day						
		40% fT > MIC	100% fT > MIC	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
0.5 mg q24h post-HD	2	97.0	29.4	97.0	97.0	97.0	97.0	97.0	96.3	97.0
	8	49.9	0.0	35.6	47.5	50.5	51.2	51.6	49.5	52.0
1g q24h post-HD	2	99.2	56.6	99.2	99.2	99.2	99.2	99.2	99.0	99.2
	8	87.9	2.5	84.7	87.7	88.0	88.0	88.0	86.3	88.0
1g LD, 0.5g q12h post-HD	2	99.9	74.0	99.9	99.9	99.9	99.9	99.9	99.9	99.9
	8	93.8	18.3	97.5	92.4	92.2	92.2	92.2	91.0	92.2

The dose in yellow or green is the smallest meropenem dosing regimen attaining PD targets of [>40% fT>MIC] and >40% [fT>4xMIC] respectively

Dosing Recommendation Results

	Type	Effluent Flow Rate	Duration	Frequency	Meropenem Dose [Less Aggressive PD Target] (40% fT>MICx1)	Meropenem Dose [More Aggressive PD Target] (40% fT>MICx4)
1	HD	Qd 300 ml/min	4-hours	M-W-F	0.5g q24h post-HD	1g LD, then 0.5g q12h post-HD
2	HD	Qd 300 ml/min	4-hours	Daily		
3	Sequential HD and UF	Qd 300 m/min Quf 5 ml/min	HD 4-hours, then UF 20-hours	Daily		
4	PIKRT	Qd 100 ml/min	9-hours	Daily	0.5g q12h	0.5g q8h
5	Extended Therapy	Qd 50 ml/min	24-hours	Daily		1g q12h

Discussion & Conclusions

- MCS analysis predicted that alterations in KRT parameters may necessitate different meropenem doses to attain efficacy targets, but recommended doses for thrice weekly HD, daily HD, and sequential HD and UF were all the same.
- MCS doses for the more aggressive PD target (40% fT>MICx4) are consistent with the latest UpToDate meropenem dosing recommendations for hemodialysis (MCS models 1-3), PIKRT (MCS model 4) and CRRT (MCS model 5). [Mueller BA, Roberts J, Heung M. Meropenem Dosing: Kidney Impairment. In: *UpToDate*, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on March 15, 2023.)]
- None of the simulated meropenem dosing regimens met PTA goals for a target of 100% fT >MIC.
- These findings need clinical validation.

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