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

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Abstract

Introduction: The Tablo Hemodialysis System offers a range of kidney replacement therapy (KRT) options for critically ill patients with AKI. The use of a variety of dialysate flow rate and treatment duration & frequencies that are available may clear drugs like cefepime differently than conventional devices. The purpose of this Monte Carlo Simulation (MCS) was to develop cefepime doses likely to attain therapeutic targets for a variety of KRT treatment combinations.

Methods: Published body weights and pharmacokinetic parameter estimates were used to develop pharmacokinetic models and to generate free cefepime plasma concentrations in 5 different KRT regimens (Table). All patients were assumed to be anuric. MCS was performed to assess the probability of target attainment (PTA) of various cefepime dosing regimens with 0.5-hour infusions. Three efficacy targets used were 1) ≥60% free plasma concentrations above the minimum inhibitory concentration (≥60% *f*T >MIC), 2) 4 time above the MIC (≥60% *f*T >4xMIC), or 3) 100% *f*T >MIC with the breakpoint MIC of 8 mg/L for *Pseudomonas aeruginosa.* In addition, the safety of each dose was assessed using a total cefepime trough concentration associated with increased risk of potential neurotoxicity (20 mg/L). The smallest doses attaining PTA ≥90% during 1-week of therapy were considered optimal.

Results: Cefepime doses attaining the three different efficacy targets in the 5 KRT settings are shown in the Table. Optimal doses attaining the aggressive efficacy targets (60% fT>MICx4 or 100% fT>MIC) yielded total trough drug concentrations exceeding the safety threshold in most (62-99%) patients.

Conclusion: MCS analysis predicted that alterations in KRT parameters may necessitate different cefepime doses to attain efficacy targets, but recommended doses for thrice weekly HD, daily HD, and sequential HD and UF were all the same. Higher cefepime doses were required to attain more aggressive pharmacodynamic targets but were likely to be associated with a higher risk of neurotoxicity. 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 cefepime 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 cefepime 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 cefepime PK parameters to predict one week of cefepime exposure in 5,000 virtual patients (>40 kg & anuric) receiving 5 different KRT regimens.
- Cefepime extraction coefficients [EC: SA or SC] were determined from all published cefepime studies using KRT. Cefepime transmembrane clearance (CL) from Tablo KRT was estimated using EC and effluent flow rates [Qeff: Qd or Quf] as follows: CL = EC x Qeff.
- Three efficacy targets used were 1) ≥60% free plasma concentrations above the minimum inhibitory concentration (≥60% fT >MIC), 2) 4 times above the MIC (≥60% fT >4xMIC), or 3) 100% fT >MIC with the breakpoint MIC of 8 mg/L for *P. aeruginosa.*
- The smallest doses attaining targets in ≥90% of subjects during 1-week of therapy were considered optimal.
- The safety of each dose was assessed using a total cefepime trough concentration associated with increased risk of potential neurotoxicity (20 mg/L).

Body Weight and Pharmacokinetic Parameters Used

Body weight (kg)	88 ± 26 [40-177]
Vd(L/kg)	0.45 ± 0.25 [0.21-1.11]
Non-renal CL (L/hr)	24.6 ± 19.4 [0-66.8]
Unbound fraction	0.79 ± 0.09 [0-1]
Extraction coefficients	Qd 300 ml/min : SA = 0.45 ± 0.09 [0-1] Qd 100 ml/min: SA= 0.68± 0.14 [0-1] Qd 50 ml/min: SA = 0.75 ± 0.15 [0-1] Quf 5 ml/min: SC = 0.82 ± 0.16 [0-1]

Qd: dialysate flow rate; Quf: ultrafiltrate flow rate;
SA: saturation coefficient; SC: sieving coefficient

Results - Sample Model 3 (Sequential Therapy)

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

Cefepime Dosing Regimen	PD Target	PTA (%) of Each Day							PTA (%) of 1-week
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	
2g LD, 1g q24h post-HD	**≥60%fT>MIC**	**98.3%**	**89.1%**	**87.8%**	**87.5%**	**87.4%**	**87.4%**	**87.4%**	**89.4**
	≥60%fT>MICx4	20.4%	2.3%	1.2%	1.0%	0.9%	0.9%	0.9%	1.5%
	100%fT>MIC	38.8%	21.6%	18.2%	17.1%	16.9%	16.9%	16.8%	16.4%
3g LD, 2g q12h post-HD	≥60%fT>MIC	100%	100%	100%	100%	100%	100%	100%	100%
	≥60%fT>MICx4	**81.8%**	**89.2%**	**90.6%**	**90.9%**	**91.0%**	**91.0%**	**91.0%**	**90.9%**
	100%fT>MIC	88.6%	87.2%	87.2%	87.2%	87.2%	87.2%	87.2%	87.2%
2g q12h post-HD	≥60%fT>MIC	100%	100%	100%	100%	100%	100%	100%	100%
	≥60%fT>MICx4	53.2%	86.2%	90.5%	91.3%	91.4%	91.4%	91.5%	88.9%
	100%fT>MIC	**85.9%**	**86.8%**	**86.8%**	**86.8%**	**86.8%**	**86.8%**	**86.8%**	**85.9%**
1g q8h post-HD	≥60%fT>MIC	99.9%	100%	100%	100%	100%	100%	100%	99.9%
	≥60%fT>MICx4	18.4%	53.2%	62.8%	67.1%	67.8%	67.8%	68.4%	62.5%
	100%fT>MIC	76.6%	81.1%	83.8%	83.9%	83.9%	85.8%	84.1%	75.1%

The dose in yellow, blue and green is the smallest cefepime dosing regimen attaining PD targets of ≥60% fT>MIC=8 mg/L, ≥60% fT>4xMIC=32mg/L, and 100% fT>MIC=8 mg/L respectively.

Results - Dosing Recommendation

	KRT Regimen				Cefepime Dosing Recommendation		
	Type	Effluent Flow Rate (ml/min)	Duration (Hours)	Frequency	≥60% fT>MIC	≥60% fT>4xMIC	100% fT>MIC
1	HD	Qd 300	4	M-W-F	2g LD, 1g q24h post-HD	3g LD, 2g q12h post-HD	2g q12h post-HD
2	HD	Qd 300	4	Daily			
3	Sequential Therapy	Qd 300 Quf 5	HD 4, then UF 20	Daily			
4	PIKRT	Qd 100	9	Daily	1g q12h	3g LD, 1g q6h	2g LD, 1g q6h
5	Extended Therapy	Qd 50	24	Daily		2g q8h	2g q12h

Discussion

- MCS predicted that cefepime doses attaining aggressive PD efficacy targets (≥ 60% fT>MICx4 or 100% fT>MIC) would increase risk of neurotoxicity.
- Unavoidably, cefepime doses attaining the aggressive efficacy targets (60% fT>MICx4 or 100% fT>MICx1) yielded total cefepime concentration exceeding the safety threshold (20 mg/L) at the end of each simulated day in many virtual patients (58-99%).

Conclusions

- MCS analysis predicted that alterations in KRT parameters may necessitate different cefepime doses to attain efficacy targets, but recommended doses for thrice weekly HD, daily HD, and sequential HD and UF were all the same.
- Higher cefepime doses were required to attain more aggressive pharmacodynamic targets but were likely to be associated with a higher risk of neurotoxicity, requiring vigilant monitoring.
- These findings need clinical validation.

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