Cefepime Dosing in Modeled Critically Ill Patients Receiving SHIFT Hemofiltration or Hemodialysis Renal Replacement Therapies

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Introduction

- Cefepime is a renally-eliminated antibiotic requiring dose adjustments in patients with kidney disease or those receiving renal replacement therapies (RRTs) due to the risk of neurotoxicity.
- Studies suggest that recommended cefepime doses of 1-2 g every 12 hours (q12h) are inadequate to meet pharmacodynamic targets in critically ill patients with acute kidney injury (AKI) receiving continuous RRTs (CRRT), necessitating higher doses in these patients. [1-2]
- SHIFT is a daily prolonged intermittent RRT used in critically ill patients with AKI as an alternative to CRRT.
- Cefepime dosing information in critically ill patients receiving SHIFT RRT is needed.

Objective

To develop initial dosing recommendations of cefepime for critically ill patients receiving SHIFT RRT by applying Monte Carlo simulations to pharmacokinetic (PK) models of SHIFT

Methods

Model

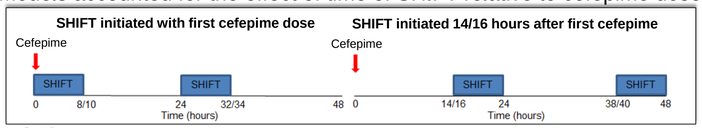
- Published PK data from studies in critically ill patients receiving CRRT were collated to determine the mean±SD of several PK parameters to input into PK models of four common modalities of SHIFT RRT [Table 1].

Methods

		Hemofiltration (HF)		Hemodialysis (HD)	
SHIFT Settings	$Q_{effluent}$	5L/h	4L/h	5L/h	4L/h
	Q_{blood}	300 mL/min			
	Duration	8 hours	10 hours	8 hours	10 hours
	Frequency	Daily			
PK Parameters Mean±SD (range limits)	Weight (kg)	86.6 ± 29.2[3] (40-∞)			
	V_d (L/kg)	0.48 ± 0.24[2,4-7] (0.16[7]-1.11[4])			
	Free Fraction	0.79 ± 0.09 (0.72-0.85)[6]			
	CL_{NR} (mL/min)	24.33 ± 11.25 (13-44)[5]			
	SC or SA	0.86 ± 0.15 (0-1)		0.62 ± 0.12 (0-1)	0.67 ± 0.13 (0-1)

Table 1. Modelled SHIFT settings and collated PK parameters applied to PK models

- Range limits and covariate relationships were identified from the data and were incorporated into the models to construct a virtual cohort with realistic PK parameters.
- SHIFT clearance data (SA) were derived from a regression analysis of published cefepime RRT studies.
- Models accounted for the effect of time of SHIFT relative to cefepime dose.



Simulation

- Monte Carlo simulation was performed to create cohorts of 5,000 virtual patients. Each cohort received a pre-specified dosing regimen of cefepime as outlined in Table 2.
- PK parameters were simulated as log-normal distributions.

Pharmacodynamic Target

- Free cefepime concentration ≥ 4 × minimum inhibitory concentration (MIC) of *Pseudomonas aeruginosa* (8 mg/L) for ≥ 60% of the dosing interval (60% *f*T ≥ MIC×4)

Optimal Dosing Regimen

- Probability of target attainment (PTA) ≥ 90% during the first 48 hours (0-48h) of antibiotic therapy
- 48-hour trough concentration <100 mg/L to reduce risk for neurotoxicity [8-9]

Results

Cefepime Dosing Regimen	8-Hour SHIFT Hemodialysis Initiated at T0		8-Hour SHIFT Hemodialysis Initiated at T16	
	PTA (0-48h)	48-Hour Trough Probability >100 mg/L	PTA (0-48h)	48-Hour Trough Probability >100 mg/L
1g every 6h	0.732	0	0.748	0
2g LD, 1g every 6h	0.860	0	0.890	0
3g LD, 1g every 6h	**0.930**	**0**	**0.954**	**0**
1g every 8h	0.364	0	0.376	0
1g every 8h EI	0.349	0	0.404	0
2g every 8h	**0.970**	**0.119**	**0.954**	**0**
2g every 8h EI	**0.973**	**0.208**	**0.947**	**0**
1g every 12h	0.006	0	0.042	0
1g every 12h EI	0.004	0	0.034	0
2g every 12h	0.665	0	0.772	0
2g every 12h EI	0.720	0	0.723	0
3g LD, 2g every 12h	0.812	0	0.910	0
2g LD, 2g Pre & 2g Post	0.725	0	0.622	0
3g LD, 2g Pre & 2g Post	0.847	0	0.829	0
2g LD, 4g CI	**0.912**	**0.039**	**0.923**	**0**

Table 2. Probability of target attainment (PTA) of various dosing regimens of cefepime against a MIC of 8 mg/L and the probability of a 48-hour trough concentration >100 mg/L for these regimens in the first 48 hours of antibiotic therapy when administered with 8-hour SHIFT hemodialysis. Optimal regimens achieve a PTA (0-48h) ≥ 90% in all settings of SHIFT (bold) while minimizing 48-hour trough concentrations [data illustrative of all modelled SHIFT settings].

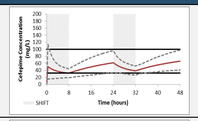
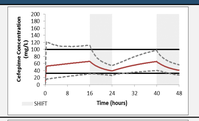
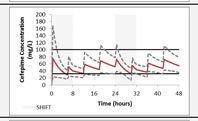
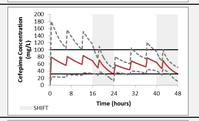
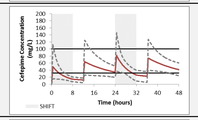
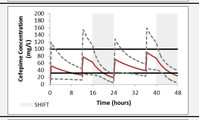
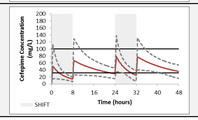
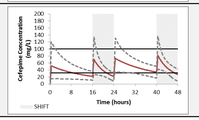
Dosing Regimen	8-Hour SHIFT Hemodialysis Initiated at T0	8-Hour SHIFT Hemodialysis Initiated at T16
2g LD, 4g CI		
3g LD, 1g q6h		
2g q12h		
2g Pre, 2g Post		

Figure 2. Simulation of select cefepime dosing regimens during the first 48 hours of therapy when 8-hour SHIFT hemodialysis is initiated with the first dose (T0) or maximally apart from the first dose (T16). Red line: mean cefepime concentration; black lines: target concentration (4×MIC for *P. aeruginosa*) and suggested maximum tolerated concentration[8-9]; dashed lines: 5-95% percentiles.

Conclusion

- A 2-3g loading dose of cefepime followed by 4g continuous infusion or 1g every 6h yields pharmacodynamic target attainment for most modelled critically ill patients receiving 8 or 10 hours of SHIFT hemofiltration or hemodialysis while minimizing trough concentrations in the first 48 hours of antibiotic therapy.
- A loading dose is necessary to attain the pharmacodynamic target early in the course of antibiotic therapy.
- Future clinical studies should be conducted to validate these findings.

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Acknowledgements

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