Identification of Optimal Ceftazidime Dosing Regimens in Modeled Critically Ill Patients Receiving SHIFT Renal Replacement Therapy

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Introduction

- Ceftazidime is a renally-eliminated antibiotic that requires dose adjustments in critically ill patients with acute kidney injury (AKI).
- Pharmacokinetic (PK) studies suggest that patients with AKI receiving continuous renal replacement therapy (CRRT) may require the same dose or even higher doses of ceftazidime as those without renal failure [1-4].
- No published ceftazidime dosing recommendations currently exist for critically ill patients receiving SHIFT renal replacement therapy (RRT), a daily prolonged intermittent RRT used as an alternative to CRRT.

Objective

To identify optimal ceftazidime dosing regimens in critically ill patients receiving SHIFT RRT by applying Monte Carlo simulations to pharmacokinetic (PK) models of SHIFT

Methods

Model

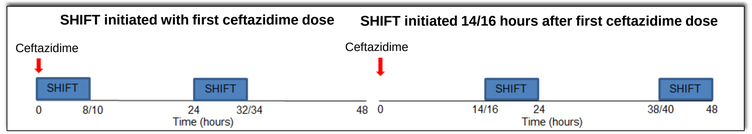
- Published PK data from studies in critically ill patients receiving ceftazidime with CRRT were collated to determine the mean±SD of several PK parameter to input into PK models of four common modalities of SHIFT RRT [Table 1].
- Range limits and covariate relationships were identified from the data and were incorporated into the models to construct a virtual cohort with realistic PK parameters.

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[5] (40-∞)			
	V_d (L/kg)	0.34 ± 0.20[3,4,6-8] (0.13-1.1)[4,7]			
	Free Fraction	0.86 ± 0.05[6,7] (0.75-0.94)[7]			
	CL_{NR} (mL/min)	15.9 ± 9.9[3,6-9] (8-37.7)[6,7]			
	SC or SA	0.68 ± 0.14 (0-1)		0.53 ± 0.11 (0-1)	0.46 ± 0.09 (0-1)

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

- SHIFT clearance data (SC and SA) were derived from a regression analysis of published ceftazidime RRT studies.
- Models accounted for the effect of time of SHIFT relative to ceftazidime dose.



Simulation

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

Pharmacodynamic Target

- Free ceftazidime 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 [10-11]

Results

Dosing Regimen	8-Hour SHIFT Hemodialysis Initiated at T0		8-Hour SHIFT Hemodialysis Initiated at T16	
	PTA (0-48h) (60% fT ≥ MIC×4)	48-Hour Trough Probability >100 mg/L	PTA (0-48h) (60% fT ≥ MIC×4)	48-Hour Trough Probability >100 mg/L
1g every 6h	**0.9754**	**0.235**	**0.9576**	**0**
2g LD, 1g every 6h	**0.9896**	**0.25**	**0.9878**	**0**
1g every 8h	0.8654	0.018	0.8396	0
1g every 8h EI	0.8714	0.054	0.8378	0
2g LD, 1g every 8h	**0.9568**	**0.019**	**0.96**	**0**
2g every 8h	**0.999**	**0.67**	**0.9982**	**0.05**
2g every 8h EI	**0.9986**	**0.759**	**0.9974**	**0.114**
1g every 12h	0.3424	0	0.4476	0
1g every 12h EI	0.3146	0	0.3804	0
2g every 12h	**0.97**	**0.046**	**0.979**	**0**
2g every 12h EI	**0.9796**	**0.132**	**0.9662**	**0**
2g LD, 2g Pre & 1g Post	0.7882	0	0.9006	0
2g LD, 2g Pre & 2g Post	**0.9718**	**0.011**	**0.9598**	**0**
2g LD, 3g CI	**0.9776**	**0.176**	**0.9832**	**0**

Table 2. Probability of target attainment (PTA) of various dosing regimens of ceftazidime 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].

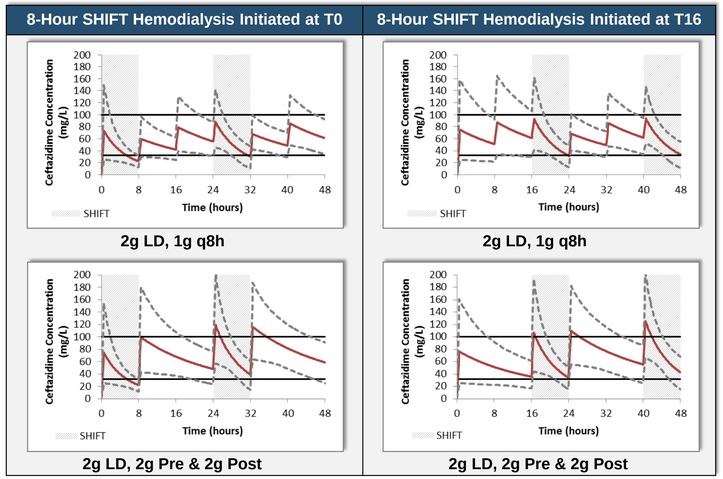


Figure 2. Simulation of select ceftazidime dosing regimens during the first 48 hours of therapy when 8-hour SHIFT hemodialysis is initiated with the first dose (T0) or maximally apart from the first dose (T16). Red line: mean ceftazidime concentration; black lines: target concentration (4×MIC for *P.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

Conclusion

- A 2g loading dose of ceftazidime followed by 1g q8h or 2g pre-SHIFT and 2g post-SHIFT yields pharmacodynamic target attainment for most modelled critically ill patients receiving 8 or 10 hours of SHIFT RRT while minimizing trough concentrations in the first 48 hours of antibiotic therapy.
- Timing of ceftazidime dose relative to SHIFT may have a marked effect on PTA.
- Future clinical studies should be conducted to validate these findings.

References

1. Aronoff GR, et al. Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children. (5th ed.) Philadelphia: American College of Physicians. 2007.
2. Seyler L, et al. Recommended β-lactam regimens are inadequate in septic patients treated with continuous renal replacement therapy. Crit Care. 2011; 15(3):R137.
3. Mariat C, et al. Continous infusion of ceftazidime in critically ill patients undergoing continuous venovenous haemodiafiltration: pharmacokinetic evaluation and dose recommendation. Crit Care. 2006 Feb;10(1):R26.
4. Traunmüller F, et al. Clearance of ceftazidime during continuous venovenous haemofiltration in critically ill patients. J Antimicrob Chemother. 2002 Jan;49(1):129-34.
5. Gashti CN, et al. Accelerated venovenous hemofiltration: early technical and clinical experience. Am J Kidney Dis. 2008 May;51(5):804-10.
6. Vos MC, et al. Drug clearance by continuous haemodiafiltration: Results with the AN-69 capillary haemofilter and recommended dose adjustments for seven antibiotics. Drug Invest. 1994;7(6):315-322.
7. Isla A, et al. In vitro AN69 and polysulphone membrane permeability to ceftazidime and in vivo pharmacokinetics during continuous renal replacement therapies. Chemotherapy. 2007;53(3):194-201.
8. Kinowski JM, et al. Multiple-dose pharmacokinetics of amikacin and ceftazidime in critically ill patients with septic multiple-organ failure during intermittent hemofiltration. Antimicrob Agents Chemother. 1993 Mar;37(3):464-73.
9. Joos B, et al. Pharmacokinetics of antimicrobial agents in anuric patients during continuous venovenous haemofiltration. Nephrol Dial Transplant. 1996 Aug;11(8):1582-5.
10. Moriyama B, et al. Continuous-infusion beta-lactam antibiotics during continuous venovenous hemofiltration for the treatment of resistant gram-negative bacteria. Ann Pharmacother. 2009 Jul;1324-37.
11. Georges B, et al. Ceftazidime dosage regimen in intensive care unit patients: from a population pharmacokinetic approach to clinical practice via Monte Carlo simulations. Br J Clin Pharmacol. 2012 Apr;73(4);588-96.

Acknowledgements

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