

Monte Carlo Simulations to Determine Optimal Levofloxacin Dosing for Gram Negative Infections in Patients Receiving SHIFT Renal Replacement Therapy

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Abstract 71



Introduction

- SHIFT is a daily 8-10 hour renal replacement therapy (RRT) for treating acute kidney injury in critically ill patients.
- The recommended antibiotic dosing regimens from the published literature resulted in subtherapeutic concentrations in critically ill patients receiving RRT. [1]
- Monte Carlo Simulation (MCS) can be used to predict the optimal antibiotic dosing regimens to treat infectious diseases in critically ill patients receiving RRT. [2]
- Levofloxacin is commonly used for community-acquired pneumonia, skin and soft tissue infections, and complicated urinary tract infections in critically ill patients. [3]
- At higher levofloxacin doses (maximum dose of 750 mg daily), cardio- and neurotoxicity can occur [4]; doses are recommended to be reduced in renal disease.[5,6]
- Since no published levofloxacin dosing regimens currently exist for critically ill patients receiving SHIFT RRT, its dosing recommendation in critically ill patients receiving SHIFT RRT is required.

Objective

To develop initial dosing recommendations of levofloxacin for Gram negative infections in critically ill patients receiving SHIFT RRT by applying MCS to pharmacokinetic and pharmacodynamic models of SHIFT.

Methods

Mathematical Pharmacokinetic Model Development

- A one compartment and first order elimination pharmacokinetic model with daily SHIFT RRT instituted for 8 or 10 hours was created to predict levofloxacin deposition for 72 hours of initial therapy.
- Published levofloxacin pharmacokinetic data and associated variability obtained from critically ill patients were used to develop models for virtual patients receiving daily SHIFT RRT using four different modalities. [Table 1]
- Daily SHIFT RRT regimen was modelled to be initiated either at the beginning of (early SHIFT) or 14-16 hours after initial drug administration (late SHIFT) to ensure a broad range of clinical scenarios.

Figure 1. Daily SHIFT RRT Settings Occurring at 2 Different Times Relative to Levofloxacin Dose



- Range limits and correlation on input parameters estimated from the data were included in the models to construct a virtual cohort with population-specific pharmacokinetic parameters.

Table 1. Input Parameters Used in Monte Carlo Simulation Trials [7-9]

Daily SHIFT Settings	Hemofiltration	Hemodialysis		
		5L/h	4L/h	5L/h
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			
Pharmacokinetic Parameters	Weight (kg)	86.6 ± 29.2 (40,∞)		
Mean±SD	V_d (L/kg)	1.2±0.4 (0.7,2.08)		
(range limits)	CL_{NR} (mL/min)	25.7±14 (0.12,67)		
	SC or SA	0.6±0.2 (0,1)		

Monte Carlo Simulation

- MCS generated drug concentration profiles for each regimen in a different group of 5,000 virtual patients.
- Twelve levofloxacin regimens, including the recommended doses from published resources for critically ill patients receiving CRRT, intermittent hemodialysis and patients with normal renal function were simulated. [Table 2]

Prediction of Probability of Target Attainment (PTA)

- The PTA was evaluated by the average daily area under the total levofloxacin concentration-time curve (AUC_{24h}) of ≥ 125 to the minimum inhibitory concentration (MIC) of 2 mg/L (MIC for sensitive *Pseudomonas aeruginosa*) for the first 72 hours of therapy. [10-12]
- The optimal regimen was defined as occurring when $\geq 90\%$ of virtual patients attained PTA with the lowest daily dose to decrease toxicity risk.

Results

- All modalities (hemodialysis, hemofiltration) and settings (8- or 10-hour SHIFT RRT) showed similar results.
- Attainment of $\geq 90\%$ PTA required levofloxacin doses of $>3,000$ mg/day in all daily SHIFT models during the initial 72 hours of therapy (Figure 2 displays the PTA results of late 8-hour SHIFT hemodialysis as a representative modality).
- No FDA-approved doses used in this study achieved PTA.
- A regimen with an extremely high loading dose and post-SHIFT dosing was the only regimen found to yield a PTA of $\geq 90\%$ with the lowest total daily dose.

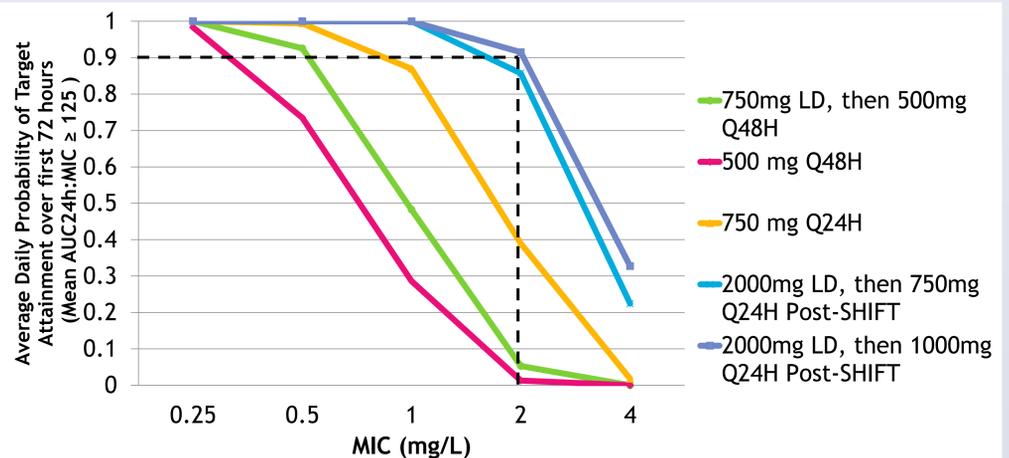
Results (continued)

Table 2. Average Daily PTA over 72 hours in 5000 Virtual Patients Receiving 8-Hour SHIFT Hemodialysis with Different Levofloxacin Regimens

Dosing	Early SHIFT RRT	Late SHIFT RRT
	PTA (Mean $AUC_{24h}/MIC > 125$)	PTA (Mean $AUC_{24h}/MIC > 125$)
500 mg Q 48 H	0.00	0.01
750 mg Q 24 H	0.24	0.39
750 mg LD, then 500 mg Q 48 H	0.01	0.05
750 mg LD, then 250 mg Q 48 H Post SHIFT	0.06	0.05
750 mg LD, then 500 mg Q 48 H Post SHIFT	0.17	0.10
750 mg LD, then 250 mg Q 24 H Post SHIFT	0.05	0.05
750 mg LD, then 500 mg Q 24 H Post SHIFT	0.31	0.20
750 mg LD, then 750 mg Q 24 H Post SHIFT	0.62	0.39
1500 mg LD, then 750 mg Q 24 H Post SHIFT	0.84	0.73
1500 mg LD, then 1000 mg Q 24 H Post SHIFT	0.93	0.81
2000 mg LD, then 750 mg Q 24 H Post SHIFT	0.92	0.86
2000 mg LD, then 1000 mg Q 24 H Post SHIFT*	0.97	0.92

*the lowest dosing regimen yielding $\geq 90\%$ PTA

Figure 2. PTA of Selected Levofloxacin Regimens at Different MICs in Patients Receiving 8-Hour Late SHIFT Therapy with Hemodialysis



Discussion/Conclusion

- This is the first study using MCS to identify the optimal dose of levofloxacin for Gram negative infections in critically ill patients receiving SHIFT RRT.
- MCS with literature-based demographic and PK data from critically ill patients can be a powerful tool to predict the drug concentration profiles and antibiotic dosing in critically ill patients receiving SHIFT RRT.
- A 2,000 mg levofloxacin loading dose with 1,000 mg q 24 hours post-SHIFT achieved the PTA for all SHIFT settings, but this simulated regimen exceeds the maximum dose for patients with normal renal function and is likely to be toxic.
- No conventional levofloxacin doses could achieve the PTA target for optimum efficacy in these patients.
- Using levofloxacin in patients with SHIFT RRT cannot be recommended as monotherapy for Gram negative infections.

References

1. Seyler L, et al. *Crit Care*. 2011; 15(3):R137.
2. Goldstein S, et al. *Pediatr Nephrol*. 2001; 16: 1015-8.
3. Rebeck JA, et al. *Pharmacotherapy*. 2002; 22(10): 1216-25.
4. Lannini PB. *Expert Opin Drug Safety*. 2002; 1(2): 121-8.
5. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically.
6. Lui HH. *Drug Saf*. 2010; 33(5): 353-69.
7. Hansen E, et al. *Intensive Care Med*. 2001; 27: 371-5.
8. Malone RS, et al. *Antimicrob Agents Chemother*. 2001; 45(10): 2949.
9. Guenter SG, et al. *Pharmacotherapy*. 2002; 22(2): 175-83.
10. Clinical and Laboratory Standards Institute. Wayne, PA:CLSI;2014.
11. Forrest A, et al. *Antimicrob Agents Chemother*. 1993; 37(5): 1073-81.
12. Craig WA. *Clin Infect Dis*. 1998;26(1):1-10.

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