

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

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Abstract 70

Introduction

- Ciprofloxacin is commonly used in the intensive care units for treatment of nosocomial infections.¹
- Ciprofloxacin is a renally-eliminated antibiotic that requires dose adjustment in patients with kidney disease or critically ill patients receiving renal replacement therapy.²
- Pharmacokinetic (PK) studies suggest that critically ill patients receiving renal replacement therapy often do not meet pharmacokinetic and pharmacodynamic targets.³⁻⁵
- Due to the risk of cardio- and neurotoxicity ciprofloxacin doses should not exceed 1200 mg/day.²
- SHIFT is a prolonged intermittent renal replacement therapy that is used as an alternative to continuous renal replacement therapy.
- Monte Carlo simulations can be used to predict optimal dosage regimens in critically ill patients receiving renal replacement therapies.⁶
- No published ciprofloxacin dosing recommendations exist for critically ill patients receiving SHIFT renal replacement therapy.

Objective

To evaluate the probability of target attainment of conventional ciprofloxacin regimens and to identify optimal ciprofloxacin dosing regimens in critically ill patients receiving SHIFT renal replacement therapy.

Methods

Model

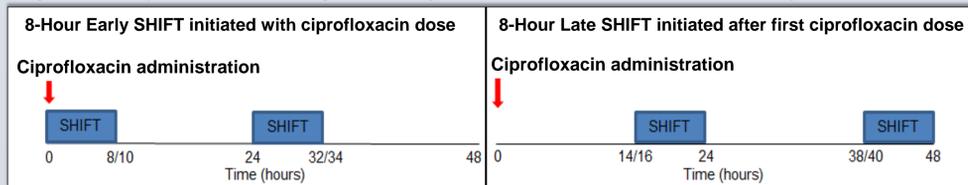
- Published ciprofloxacin pharmacokinetic data from studies in critically ill patients receiving CRRT were combined to determine the mean \pm SD of the PK parameters to input into PK models of four modalities of SHIFT renal replacement therapy [Table 1].

Table 1. Modelled SHIFT settings and PK parameters applied to PK models.^{4,7-10}

| SHIFT Settings | Hemofiltration | | Hemodialysis | |
|--|---------------------------|---------------------------------|--------------|----------|
| | 5L/h | 4L/h | 5L/h | 4L/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 | | | |
| PK Parameters Mean \pm SD (range limits) | Weight (kg) | 86.6 \pm 29.2 (40- ∞) | | |
| | V _d (L/kg) | 1.2 \pm 0.4 (0.5-1.92) | | |
| | CL _{NR} (mL/min) | 116 \pm 61 (13-259) | | |
| | SC or SA | 0.7 \pm 0.2 (0-1) | | |

- Any identified range limits and covariate relationships from the data were incorporated into the models to construct a virtual cohort with population specific PK parameters.
- A one compartment and first order elimination pharmacokinetic model incorporated daily SHIFT renal replacement therapy to predict ciprofloxacin deposition for the initial 72 hours of therapy.

Figure 1. Daily SHIFT RRT Settings Occurring at Two Different Times Relative to Ciprofloxacin Dose.



Monte Carlo Simulation

- Monte Carlo simulation was performed to create individual drug concentration profiles for cohorts of 5,000 virtual patients.
- Twelve ciprofloxacin regimens were simulated. Each of the cohorts received the pre-specified dosing regimens as shown in Table 2.

Pharmacodynamic Target

- The area under the total serum ciprofloxacin concentration time curve to the minimum inhibitory concentration (AUC/MIC) of susceptible *Pseudomonas aeruginosa* (MIC: 1 mg/L) of ≥ 125 .¹¹⁻¹²

Optimal Dosing Regimen

- Probability of target attainment (PTA) was evaluated by the fraction of virtual patients attaining the pharmacodynamic target (AUC/MIC ≥ 125) on day one and for the initial 72 hours of therapy.
- The ideal dosing regimen was defined as $\geq 90\%$ of virtual patients attaining PTA on day one and for the initial 72 hours with the lowest daily dose.

Results

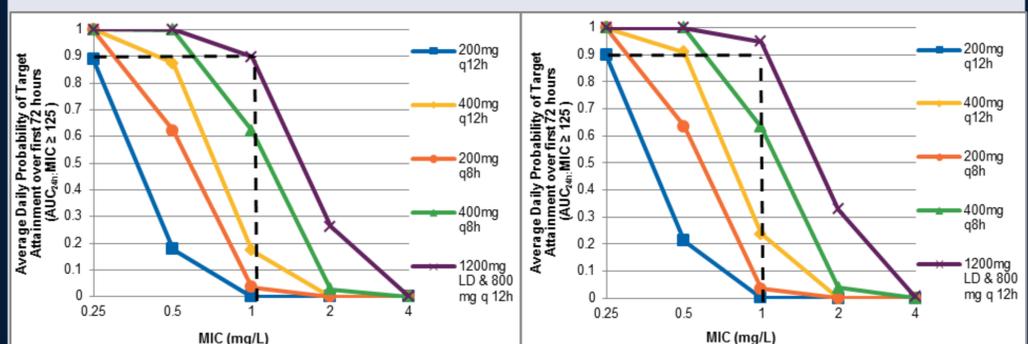
- Similar results were seen in both modalities (hemodialysis and hemofiltration) and settings (8 and 10 hour SHIFT).
- A ciprofloxacin dose ≥ 2000 mg/day is required to attain $\geq 90\%$ probability of target attainment on day 1 in all of the SHIFT models.
- A maintenance dose of ≥ 1600 mg/day is needed to maintain $\geq 90\%$ probability of target attainment on the following days.

Table 2. Probability of Target Attainment in 5000 Virtual Patients Receiving 8-hour SHIFT Hemodialysis with Ciprofloxacin Over 72 hours.

| Dose | Early SHIFT RRT | Late SHIFT RRT |
|----------------------------------|---|---|
| | PTA (Mean AUC _{0-24h} /MIC > 125) | PTA (Mean AUC _{0-24h} /MIC > 125) |
| 200 mg Q 12 H | 0.00 | 0.00 |
| 400 mg Q 12 H | 0.24 | 0.19 |
| 600 mg Q 12 H | 0.6638 | 0.65 |
| 800 mg Q 12H | 0.8788 | 0.90 |
| 1000 mg LD, then 800 mg Q 12 H* | 0.90 | 0.93 |
| 1200 mg LD, then 800 mg Q 12 H** | 0.93 | 0.95 |
| 200 mg Q 8 H | 0.0352 | 0.035 |
| 400 mg Q 8 H | 0.63 | 0.62 |
| 600 mg Q 8 H | 0.94 | 0.94 |
| 800 mg Q 8 H | 1.00 | 1.00 |
| 800 mg LD, then 600 mg Q 8 H | 0.97 | 0.97 |
| 1000 mg LD, then 600 mg Q 8 H | 0.97 | 0.99 |

*PTA $\geq 90\%$ not achieved on day 1.

**PTA $\geq 90\%$ achieved on day 1 and for the initial 72 hours



Discussion/Conclusion

- This is the first study to look at optimal ciprofloxacin dosage regimens in critically ill patients on SHIFT renal replacement therapy.
- No literature-based recommended doses attained the PTA target for 1 day or the initial 72 hours in patients receiving daily SHIFT renal replacement therapy.
- A ciprofloxacin dose consisting of a 1200 mg loading dose and a maintenance dose of 800 mg every 12 hours is required to attain the PTA target in $\geq 90\%$ of critically ill patients receiving SHIFT renal replacement therapy. This dose exceeds the maximum daily dose for patients with normal renal function and is likely to be toxic.
- Using ciprofloxacin in critically ill patients with SHIFT renal replacement therapy cannot be recommended as monotherapy and should be avoided if the presenting organism has a MIC ≥ 1 mg/L.

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