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Optimal levofloxacin dosing regimens in critically ill patients with acute kidney injury receiving continuous renal replacement therapy

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ABSTRACT

Purposes: To determine appropriate dosing of levofloxacin in critically ill patients receiving continuous renal replacement therapy (CRRT).
Methods: All necessary pharmacokinetic and pharmacodynamic parameters from critically ill patients were obtained to develop mathematical models with first order elimination. Levofloxacin concentration-time profiles were calculated to determine the efficacy based on the probability of target attainment (PTA) of AUC_{24h}/MIC ≥50 for Gram-positive and AUC_{24h}/MIC ≥125 for Gram-negative infections. A group of 5000 virtual patients was simulated and tested using Monte Carlo simulations for each dose in the models. The optimal dosing regimens were defined as the dose achieved target PTA at least 90% of the virtual patients.
Results: No conventional, FDA approved regimens achieved at least 90% of PTA for Gram-negative infection with *Pseudomonas aeruginosa* at MIC of 2 mg/L. The successful dose (1750 mg on day 1, then 1500 mg q 24 h) was far exceeded the maximum FDA-approved doses. For Gram-positive infections, a levofloxacin 750 mg q 24 h was sufficient to attain PTA target of ~90% at the MIC of 2 mg/L for *Streptococcus pneumoniae*.
Conclusions: Levofloxacin cannot be recommended as an empiric monotherapy for serious Gram-negative infections in patients receiving CRRT due to suboptimal efficacy.

1. Introduction

In the ICU, nearly 50% of septic patients develop acute kidney injury (AKI) and consequently require continuous renal replacement therapy (CRRT) [1]. In addition, more than two in three critically ill patients are infected and receive antibiotics, which is the main driven cause of mortality [2]. Previous research suggested that the early provision of appropriate antibiotics is important in the management of infection and improves outcomes [3]. Therefore, initial proper antibiotic dosing is crucial to minimize the mortality.

During the acute illness, physiologic changes such as increased volume distribution (Vd), decreased plasma protein binding, and increased drug clearance by CRRT affect antibiotic concentration [4]. These

Abbreviation: AKI, Acute kidney injury; CL_{HD}, Transmembrane clearance in hemodialysis; CL_{HF}, Transmembrane clearance in hemofiltration; CL_{NR}, Non-renal clearance; CLSI, Clinical Laboratory Standards Institute; CRRT, Continuous renal replacement therapy; CVVH, Continuous venovenous hemofiltration; CVVHD, Continuous venovenous hemodialysis; AUC_{24h}, 24 h area under the curve; g, Gram; $gmol^{-1}$, *gram/mol*; h, Hour; KDIGO, Kidney Disease: Improving Global Outcomes; L, Liter; kg, Kilogram; LD, Loading dose; MIC, Minimum inhibitory concentration; mg, Milligram; min, Minute; mL, Milliliter; N, Number; PTA, Probability of target attainment; q, Every; PD, pharmacodynamic; PK, pharmacokinetic; Q_{blood}, Blood flow rate; Q_d, Dialysate flow rate; Q_{plasma}, Plasma flow rate; $Q_{replacement}$, Replacement fluid flow rate; Q_{uf}, Ultrafiltrate flow rate; r^2, Population-specific correlation; SA, Saturation coefficient; SC, Sieving coefficient; SD, Standard deviation; Vd, Volume of distribution.

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