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Cefepime dosing regimens in critically ill patients receiving continuous renal replacement therapy: a Monte Carlo simulation study

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Abstract

Background: Cefepime can be removed by continuous renal replacement therapy (CRRT) due to its pharmacokinetics. The purpose of this study is to define the optimal cefepime dosing regimens for critically ill patients receiving CRRT using Monte Carlo simulations (MCS).

Methods: The CRRT models of cefepime disposition during 48 h with different effluent rates were developed using published pharmacokinetic parameters, patient demographic data, and CRRT settings. Pharmacodynamic target was the cumulative percentage of a 48-h period of at least 70% that free cefepime concentration exceeds the four times susceptible breakpoint of *Pseudomonas aeruginosa* (minimum inhibitory concentration, MIC of 8). All recommended dosing regimens from available clinical resources were evaluated for the probability of target attainment (PTA) using MCS to generate drug disposition in a group of 5000 virtual patients for each dose. The optimal doses were defined as achieving the PTA at least 90% of virtual patients with lowest daily doses and the acceptable risk of neurotoxicity.

Results: Optimal cefepime doses in critically ill patients receiving CRRT with Kidney Disease: Improving Global Outcomes (KDIGO) recommended effluent rates were a regimen of 2 g loading dose followed by 1.5–1.75 g every 8 h for Gram-negative infections with a neurotoxicity risk of < 17%. Cefepime dosing regimens from this study were considerably higher than the recommended doses from clinical resources.

Conclusion: All recommended dosing regimens for patients receiving CRRT from available clinical resources failed to achieve the PTA target. The optimal dosing regimens were suggested based on CRRT modalities, MIC values, and different effluent rates. Clinical validation is warranted.

Keywords: Cefepime, Dosing, Pharmacokinetics, Pharmacodynamics, Continuous renal replacement therapy, Critically ill patients

Background

Continuous renal replacement therapy (CRRT) is generally performed in hemodynamic unstable patients with acute kidney injury (AKI) [1]. Cefepime is an antimicrobial agent that is commonly used in critically ill patients. The low protein binding affinity (16–20%) and small volume of distribution (14–20 L) make cefepime susceptible to be removed by CRRT [2–4].

Pharmacokinetic changes in critically ill patients, such as increasing of volume of distribution and hypoalbuminemia, considerably reduce hydrophilic antimicrobial agent concentrations [5]. Consequently, we might have prescribed inadequate doses of antimicrobial agents in patients with CRRT [5] and unintentionally increase the morbidity and mortality associated with sepsis [6]. The primary aim of drug dosing in this population is to use the loading dose (LD) and adequate maintenance doses

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