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 (CRRRT) 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 CRRRT.

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 CRRRT were collated to determine the mean±SD of several PK parameter to input into PK models of four common modalities of SHIFT RRT (Table 2).
- 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.

Pharmacodynamic Target
- Free ceftazidime concentration ≥ 4 × minimum inhibitory concentration (MIC) of Pseudomonas aeruginosa (8 mg/L) for ≥ 60% of the dosing interval (60% 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

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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 6 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


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