Highest Ceftazidime Conventional Dose Given as 4-Hour Infusion is Needed in Patients Receiving CRRT with Varying Effluent Rates

University of Findlay College of Pharmacy

Pharmacy

Optimal Extended-Infusion Dosing of Ceftazidime in Critically Ill Patients Receiving Continuous Renal Replacement Therapy with Varying Effluent Rates

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INTRODUCTION

- Ceftazidime is a renally-eliminated antipseudomonal β-lactam that is commonly used in critically ill patients requiring continuous renal replacement therapy (CRRT).
- Ceftazidime exhibits time-dependent bactericidal effect, thus its efficacy can be maximized with a prolonged infusion. However, data is limited to determine the optimal ceftazidime extended-infusion dosing regimens for patients receiving CRRT with varying effluent rates.
- Monte Carlo simulation was performed to predict optimal ceftazidime extended-infusion dosing regimens in these clinical scenarios.

METHODS

Pharmacokinetic (PK) modeling

- A one compartment, first order PK model incorporated the published ceftazidime demographic and PK data in pertinent patients[1-10] to predict drug exposure in the first 48 hours of ceftazidime therapy in patients receiving continuous veno-venous hemofiltration (CVVH) with three different CRRT effluent rates (20, 30 & 45 mg/kg/h).[11]

METHODS – Cont'd

Pharmacokinetic Parameters, mean ±SD (range)	
Body Weight (kg)	86.6 ± 29.2 kg (≥40 kg)
Volume of Distribution (L/kg)	0.34 ± 0.20 (0.13-1.1)
Non-renal Clearance (mL/min)	15.9 ± 9.9 (8-37.7)
Free Fraction	0.86 ± 0.05 (0-1)

Pharmacodynamic (PD) Target

- The minimum inhibitory concentration (MIC) for susceptible *Pseudomonas aeruginosa* is 8 mg/L.[12]
- The ceftazidime PD target was the free ceftazidime serum concentration ≥ 4xMIC (=32 mg/L) for ≥60% of the first 48 hours of therapy (60% fT≥ 4xMIC).[13]
- Toxicity risk was assessed at 48 hours using the suggested toxicity threshold concentrations of >100 mg/L.[14]

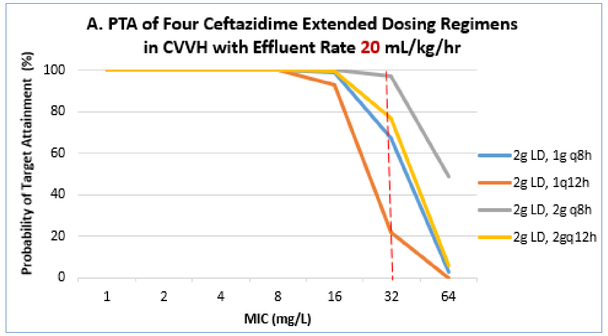
Monte Carlo Simulation (MCS)

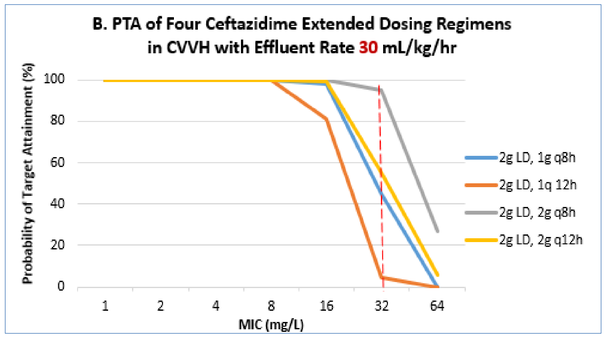
- Four different conventional dosing regimens infused over 4 hours were simulated as follows:
  - ❑ 2g loading dose (LD), then 1g q8h
  - ❑ 2g LD, then 1g q12h
  - ❑ 2g LD, then 2g q8h
  - ❑ 2g LD, then 2g q12h
- MCS generated serum ceftazidime concentration-time profiles in 5,000 virtual subjects in 0.1-hour intervals for each ceftazidime regimen.

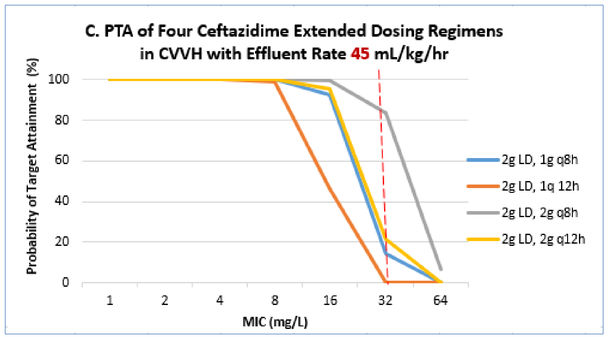
Optimal Dosing Regimen

- Probability of Target Attainment (PTA) was evaluated by the fraction of 5,000 virtual patients attaining PD target during the first 48 hours of therapy.
- Optimal doses were defined as achieving a PTA of ≥ 90% with the lowest toxicity risk.

RESULTS







DISCUSSION

- MCS predicted that only ceftazidime **2g LD, then 2 g q8h infused over 4 hours** would successfully attain ≥90% of PTA in patients receiving CVVH with effluent rates of **20 and 30 mL/kg/h**.
- However, this highest conventional dosing regimen was not sufficient to attain desirable PTA target in patients receiving CVVH with an effluent rate of **45 mL/kg/h.** Higher effluent rates would require larger extended infusion ceftazidime doses to attain PTA target.
- The toxicity risk was not significantly elevated in any of the ceftazidime dosing regimens and CVVH settings. The percentages of virtual patients with >100 mg/L at 48 hours of the highest ceftazidime dosing regimen (2g LD, then 2g q8h) were only 6%, 0.12% and 0% with an effluent rate of 20, 30, and 45 mL/kg/h respectively.
- The results of our MCS study would warrant clinical validation.

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DISCLOSURES

Authors declare no conflict of interest.

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