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Ex vivo Ceftolozane/Tazobactam Clearance during Continuous Renal Replacement Therapy

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Ceftolozane · Tazobactam · Pharmacokinetics · Clearance · Monte Carlo simulation · Continuous renal replacement therapy

Abstract
Background/Aims: To determine ceftolozane/tazobactam transmembrane clearances (CL_{TM}) in continuous hemofiltration (CHF) and continuous hemodialysis (CHD) and to determine optimal ceftolozane/tazobactam dosing regimens for patients receiving continuous renal replacement therapy (CRRT). ***Method:*** Validated, ex vivo CHF and CHD bovine blood models using polysulfone (HF1400) and AN69 (Multiflow 150-M) hemofilters were used to evaluate adsorption and CL_{TM} at different effluent flow rates. Monte Carlo simulations (MCS) using pharmacokinetic parameters from published studies and CL_{TM} from this study were used to generate ceftolozane/tazobactam dosing for patients receiving CRRT. ***Results:*** CHF and CHD CL_{TM} did not differ at equivalent effluent rates. CL_{TM} approximated effluent flow rates. No adsorption of ceftolozane/tazobactam occurred for either hemofilter. Effluent flow was the most important determinant of MCS-derived doses. ***Conclusion:*** CRRT clearances of ceftolozane/tazobactam depended on effluent flow rates but not hemofilter types. MCS-derived ceftolozane/tazobactam doses of 750 (500/250)–1,500 (1,000/500) mg every 8 h met pharmacodynamic targets for virtual patients receiving CRRT at contemporary effluent rates.

Introduction

Ceftolozane/tazobactam (Zerbaxa, Merck & Co.; formerly known as CXA-101 and FR264205), a novel cephalosporin/beta-lactamase inhibitor combination, is one of the few antibiotics effective against multi-drug resistant strains of *Pseudomonas aeruginosa* and many extended spectrum beta-lactamase (ESBL) -producing Gram-negative bacilli [1–3]. It was approved as a fixed 2:1 combination ratio of ceftolozane and tazobactam by the US Food and Drug Administration for the treatment of complicated urinary tract infections and complicated intra-abdominal infections in combination with metronidazole [4]. More recently, ceftolozane/tazobactam has been evaluated for the treatment of nosocomial pneumonia in patients with normal and impaired renal function [5].

A previous pharmacokinetic study showed that ceftolozane/tazobactam doses in patients with moderate to severe renal impairment (estimated creatinine clearance 30–59 and 15–29 mL/min, respectively) and those

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