Ceftolozane/Tazobactam Clearance During In Vitro Continuous Renal Replacement Therapy

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Introduction

- Ceftolozane/tazobactam (Zerbaxa, Merck & Co.), a novel cephalosporin/beta-lactamase inhibitor combination, is one of the few antibiotics effective against MDR strains of *Pseudomonas aeruginosa* and many ESBL-producing Gram-negative bacilli. [1-3]
- A previous study demonstrated that doses of both drugs need to be reduced in patients with renal impairment and dialysis removes 66% and 55% of ceftolozane and tazobactam area under the concentration-time curve, respectively [4].
- Ceftolozane/tazobactam are relatively small molecules (molecular weights of 666.7 vs. 322.2 Da) with similar small volumes of distribution (13.5 vs. 18.2 liters) and low plasma protein binding rates (16-21% vs. 30%) suggesting that their clearances will be affected by continuous renal replacement therapy (CRRT) [5-7].

Objective

- To determine ceftolozane/tazobactam (C/T) transmembrane clearances (CL_{TM}) and membrane adsorption in continuous hemofiltration (CHF) and continuous hemodialysis (CHD).

Methods

- Validated in vitro CHF and CHD models were performed to assess drug clearances with different combinations of hemofilter types and effluent flow rates [8-11].
- Two types of commonly-used hemofilters were used in this study; the Prismaflex HF1400 hemofilter (polyacrylethersulfone, Gambro, surface area 1.4 m^2) and Multiflow M150 hemofilter (acrylonitrile, Gambro, 1.5 m^2).

Methods

- Ceftolozane and tazobactam were added to 1 liter of pH regulated, continuously stirred, maintained at 37°C and citrated-anticoagulated bovine blood to yield final concentrations of ~70 mg/L and ~18 mg/L, respectively. These concentrations are the expected peak plasma concentrations following administration of the recommended dose [5]. Urea was added to achieve a BUN ~75 mg/dL as a control solute. Each experiment was repeated 6 times with a new hemofilter and tubing set.
- **Adsorption/degradation experiments** [12-13]: Adsorption was measured using CHF modality with a blood flow rate of 200 mL/min and an ultrafiltrate rate of 33 mL/min. Blood samples were collected from the pre-filter port at 0, 5, 10, 20 and 60 min and an ultrafiltrate sample from the ultrafiltrate port at 60 min. For degradation experiments, drugs and urea were added into the blood that was prepared with the aforementioned technique in a flask. Blood samples were obtained from the flask at the same time points as the adsorption experiments.
- **CRRT methods** [8-11]: CHF was performed with the settings of ultrafiltrate rates of 16, 33, 50 mL/min and a blood flow rate of 200 mL/min, while CHD was performed with dialysate rates 16, 33, 50, and 100 mL/min and the same blood flow. Blood and ultrafiltrate/spent dialysate samples were taken from pre- and post-hemofilter and ultrafiltrate/spent dialysate ports after the machine performed for 5 min.
- **Statistical analysis:** Student's t test and analysis of variance (ANOVA) were used to compare differences between the two hemofilters and within each hemofilter type, respectively. Power analysis indicated that six hemofilters were needed to show a 25% difference in clearance between hemofilter types.

Results

Table 1. Sieving coefficients of ceftolozane/tazobactam and urea during CHF experiments

Ultrafiltrate Flow Rate (mL/min)	HF 1400 (n=6) (mean+SD)			M 150 (n=6) (mean+SD)		
	Ceftolozane	Tazobactam	Urea	Ceftolozane	Tazobactam	Urea
16	1.05±0.08	1.31±0.09	0.90±0.17	1.02±0.15	1.27±0.21	0.90±0.27
33	1.02±0.18	1.13±0.33	0.92±0.20	1.04±0.08	1.29±0.13	1.00±0.02
50	1.01±0.09	1.28±0.14	0.94±0.05	1.02±0.08	1.30±0.18	1.03±0.12
No statistically significant differences occurred between hemofilter types or ultrafiltrate flow rates.						

Results

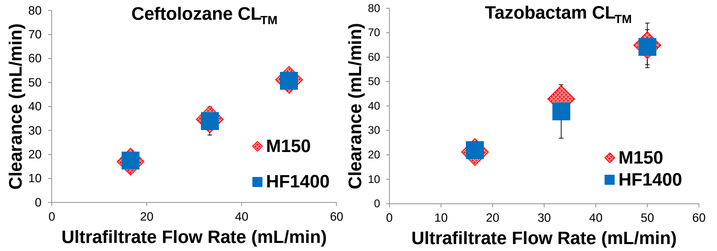

Fig. 1. Ceftolozane and tazobactam CL_{TM} during CHF (mean+SD)

Table 2. Saturation coefficients of ceftolozane/tazobactam and urea during CHD experiments

Dialysate Flow Rate (mL/min)	HF 1400 (n=6) (mean+SD)			M 150 (n=6) (mean+SD)		
	Ceftolozane	Tazobactam	Urea	Ceftolozane	Tazobactam	Urea
16	0.98±0.21	1.17±0.16	1.04±0.08	1.04±0.15	1.20±0.10	1.02±0.04
33	1.02±0.26	1.28±0.20	1.07±0.12	0.90±0.27	1.09±0.29	1.14±0.05
50	0.91±0.25	1.26±0.26	1.05±0.28	1.03±0.26	1.32±0.34	1.11±0.19
100	0.86±0.13	1.24±0.16	1.22±0.04	0.70±0.15	1.10±0.21	1.18±0.16
No statistically significant differences occurred between hemofilter types or dialysate flow rates.						

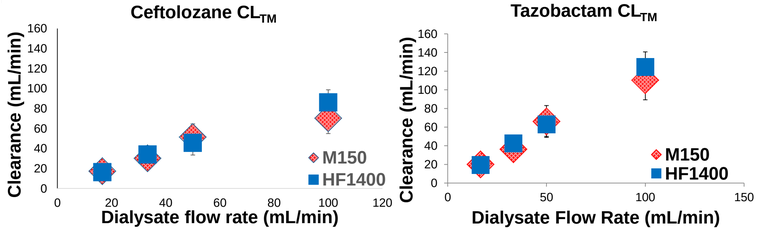

Fig. 2. Ceftolozane and tazobactam CL_{TM} during CHD (mean+SD)

Conclusion

- C/T CL_{TM} did not differ between CHF or CHD at equivalent effluent rates no matter what hemofilter was used. Significant adsorption did not occur in the model.
- C/T CHF and CHD CL_{TM} showed a strong relationship between effluent flow rates and extracorporeal drug clearances.
- C/T CRRT clearances with commonly prescribed CRRT effluent rates (30-50 mL/min) are approximately 90%/25% (respectively) of reported non-renal C/T clearance values in anuric patients [4].
- Dosage adjustment is likely necessary for CRRT because both agents are readily cleared by CRRT and their volumes of distributions are small.

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Acknowledgements

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