Ex Vivo Rezafungin Adsorption and Clearance During Continuous Hemofiltration

Soo Min Jang[1], Grayson Hough[2], Bruce A. Mueller[1]

[1]Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor, MI
[2]Cidara Therapeutics, San Diego, CA

Introduction

- Systemic fungal infections represent a serious clinical complication in patients requiring RRT in the intensive care unit setting.[1]
- Inadequate antifungal dosing may lead to both treatment failure and resistance development.[2-3]
- Echinocandins are considered first-line antifungal therapy for invasive candidiasis, especially in critically ill patients.[4]
- Rezafungin is a novel, long-acting echinocandin entering Phase 3 trials.
- Rezafungin's volume of distribution (35 L), molecular weight (1,285 Da) and plasma protein binding (97-99%) suggest that it would not be removed by continuous renal replacement therapy.[5]
- Anidulafungin, an antifungal with a similar chemical structure to rezafungin is known to bind to CRRT membranes.[6]

Objective

- To determine adsorption and transmembrane clearances (CL_{TM}) of rezafungin in continuous hemofiltration (CHF).

Methods

- Experiments using validated *ex vivo* CHF models were performed to assess drug clearances with different combinations of hemofilter types and effluent flow rates.
- Two types of commonly-used hemofilters were used in this study:
  - Prismaflex HF1400 hemofilter (polysulfone, Baxter, surface area 1.4 m^2)
  - Multiflow M150 hemofilter (acrylonitrile, Baxter, surface area 1.5 m^2)
- Rezafungin was added to 1 liter of pH regulated, continuously stirred, 37°C and citrated-anticoagulated bovine blood to yield final concentrations of ~30 mg/L.
- 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[7-10]:

- Adsorption was measured using CHF with a blood flow rate of 200 mL/min and an ultrafiltrate (UF) rate of 33 mL/min.

  Blood samples were collected from the pre-filter port at 0, 5, 10, 20 and 60 min and an UF sample from the UF port at 60 min.
- Degradation was determined by adding rezafungin and urea to the bovine blood that was prepared with the aforementioned technique. Urea does not bind and served as a control. Blood samples were obtained at the same time points as the adsorption experiments. Concentrations of both solutes at end of an hour were compared to initial concentrations.

CHF method[7-10]:

- CHF was performed with UF rates of 16, 33, 50 mL/min and a blood flow rate of 200 mL/min. Blood and UF samples were taken from pre- and post-hemofilter and UF ports. The Figure illustrates CHF circuit.
- Sieving coefficients (SC) = $\frac{C_{ultrafiltrate}}{(C_{prefilter}+C_{postfilter})/2}$
- CL_{TM} was calculated by SC × ultrafiltration rate.

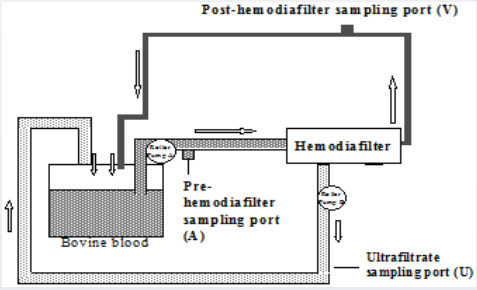
Statistical analysis:

- 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.

Rezafungin assay:

- Rezafungin concentrations were measured by LC-MS/MS with a calibration range between 0.5 to 50 mg/L and a percent coefficient of variation between 1.88% to 12.8%.

Figure. Schematic of the *ex vivo* continuous hemofiltration system



Results

- No rezafungin degradation was observed after 1-hour in blood at 37°C.
- Neither rezafungin nor urea adsorption was observed with either hemofilter type.
- Urea SC consistently approximated 1 and urea CL_{TM} was dependent on ultrafiltrate production rate.
- Rezafungin SC values were zero with three different ultrafiltrate flow rates in both hemofilter types.
- This *ex vivo* study indicates rezafungin is not cleared by CHF either by CL_{TM} or by adsorption.
- The change in UF rates and types of hemofilter did not influence the CL_{TM} (p-value >0.05).

Table. Sieving coefficients of rezafungin and urea during CHF experiments

Ultrafiltrate Flow Rate (mL/min)	HF 1400 (n=6) (mean±SD)		M 150 (n=6) (mean±SD)	
	Rezafungin	Urea	Rezafungin	Urea
16	Zero	1.0±0.1	Zero	1.0±0.1
33	Zero	1.0±0.1	Zero	1.0±0.1
50	Zero	1.0±0.1	Zero	1.0±0.1
No statistically significant differences occurred between hemofilter types or ultrafiltrate flow rates.				

Discussion/Conclusion

- No dosage adjustment for CRRT is necessary for currently marketed echinocandins (caspofungin, micafungin, anidulafungin) due to high protein binding and predominant non-renal clearance.[11-13]
- Probable anidulafungin binding to CRRT membranes was observed in a clinical trial (n=10) when pre- and post-filter anidulafungin concentrations were compared, even though no drug was detected in the ultrafiltrate.[6]
- Even though anidulafungin and rezafungin have similar chemical structure, our study findings did not detect rezafungin hemofilter binding and no measurable drug CL_{TM}.
- Rezafungin is unlikely to be adsorbed or cleared by any form of CRRT.
- Rezafungin is administered once weekly and dosage adjustment is not likely to be required for critically ill patients receiving CRRT.

References

1. Leroy O, et al. Crit Care Med 2009;37:1612-1618.
2. Sinnollareddy M, et al. Int J Antimicrob Agents 2012;39:1-10.
3. Sinnollareddy MG, et al. Crit Care 2015;19:33.
4. Pappas PG, et al. Clin Infect Dis 2016;62:e1-50.
5. Sandison T, et al. Antimicrob Agents Chemother 2017;61.
6. Leitner JM, et al. J Antimicrob Chemother 2011;66:880-884.
7. Churchwell MD, et al. Blood Purif 2006;24:548-554.
8. Stevenson JM, et al. Int J Artif Organs 2008;31:1027-1034.
9. Vilay AM, et al. Blood Purif 2010;30:37-43.
10. Lewis SJ, et al. Blood Purif 2015;40:66-71.
11. Roger C, et al. Clin Pharmacokinet 2017;56:1057-1068.
12. Vossen MG, et al. Antimicrob Agents Chemother 2017;61.
13. Agular G, et al. J Antimicrob Chemother 2014;69:1620-3.

Funding: This study was funded by Cidara Therapeutics