**Ex Vivo Rezafungin Adsorption and Clearance During Continuous Hemofiltration**

Soo Min Jang¹, Grayson Hough², Bruce A. Mueller¹

¹Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor, MI
²Cidara 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.⁵
- 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 m²)
  - Multiflow M150 hemofilter (acrylonitrile, Baxter, surface area 1.5 m²)
- 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 x 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.

---

**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

<table>
<thead>
<tr>
<th>Ultrafiltrate Flow Rate (mL/min)</th>
<th>HF 1400 (n=6) (mean±SD)</th>
<th>M 150 (n=6) (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rezafungin</td>
<td>Urea</td>
</tr>
<tr>
<td>16</td>
<td>Zero</td>
<td>1.0±0.1</td>
</tr>
<tr>
<td>33</td>
<td>Zero</td>
<td>1.0±0.1</td>
</tr>
<tr>
<td>50</td>
<td>Zero</td>
<td>1.0±0.1</td>
</tr>
</tbody>
</table>

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**


**Funding:** This study was funded by Cidara Therapeutics.