Ceftolozane/Tazobactam Clearance During In Vitro Continuous Renal Replacement Therapy

W. CHAJAMORIN1,2, A.R. SHAW1, S.J. LEWIS3, B.A. MUELLER1
1Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor, MI; 2Faculty of Pharmacy, Siam University, Bangkok, Thailand; 3College of Pharmacy, Findlay University, Findlay, OH

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 666.5 vs. 322 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 (CLTm) 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 (polyacrylonitrile) and Multiflow M150 hemofilter (acyrlynyltetrafluoroethylene, Gambro, surface area 1.4 m² and Multiflow M150 hemofilter (acyrlynyltetrafluoroethylene, Gambro, 1.5 m²).

Results

Table 1: ceftolozane/tazobactam and urea during CHF experiments

<table>
<thead>
<tr>
<th>Dialysate Flow Rate (mL/min)</th>
<th>HF 1400 (mL/min)</th>
<th>M 150 (mL/min)</th>
<th>Tazobactam CLTm (mL/min)</th>
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</thead>
<tbody>
<tr>
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<td>Tazobactam</td>
<td>Urea</td>
<td>Tazobactam</td>
</tr>
<tr>
<td>16</td>
<td>0.98±0.21</td>
<td>1.17±0.16</td>
<td>1.04±0.08</td>
</tr>
<tr>
<td>33</td>
<td>1.02±0.26</td>
<td>1.28±0.20</td>
<td>1.07±0.12</td>
</tr>
<tr>
<td>50</td>
<td>0.91±0.25</td>
<td>1.26±0.25</td>
<td>1.05±0.28</td>
</tr>
<tr>
<td>100</td>
<td>0.86±0.13</td>
<td>1.24±0.16</td>
<td>1.20±0.04</td>
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Table 2: Saturation coefficients of ceftolozane/tazobactam and urea during CHF experiments

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No statistically significant differences occurred between hemofilter types or effluent flow rates.

Conclusions

• C/T CLTm 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 CLTm 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-CRRT C/T clearances in murine systems [4].
• Dosage adjustment is likely necessary for CRRT because both agents are readily cleared by CRRT and their volumes of distribution are small.

References


Acknowledgements

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