Ex vivo characterisation of effects of renal replacement therapy modalities and settings on pharmacokinetics of meropenem-vaborbactam

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Background

• Meropenem/vaborbactam (Vabomere®) is a novel agent with activity against KPC-producing carbapenem resistant Enterobacteriaceae (CRE)1
• Vaborbactam® is now approved (FDA, 2017) for the management of complicated urinary tract infections.
• Ongoing trials show promising advantages for KPC-producing CRE infections2
• CRE infections are severe predisposing patients for sepsis and acute kidney injury requiring renal replacement therapy3

Aims

• To estimate the extent of adsorption of meropenem and vaborbactam within a clinically used continuous venovenous hemofiltration (CVVH) circuit system
• To describe the effect of point of dilution and a range of common CVVH settings on the extracorporeal removal of meropenem and vaborbactam.

Methods

Ex vivo CRRT model

\[
\text{% drug remaining} = \left( \frac{\text{Initial Concentration}}{\text{Measured Concentration}} \right) \times 100
\]

\[
\text{Extracorporeal clearance} = \frac{\text{Effluent drug concentration}}{\text{Effluent flow rate}} \times \frac{\text{Initial Concentration}}{\text{Initial drug concentration}}
\]

\[
\text{sieving coefficient} = \frac{\text{Pre-filter drug concentration}}{\text{Post-filter drug concentration}}
\]

\[
\text{\% adsorbed} = \left( \frac{\text{drug loss by adsorption}}{\text{drug loss by degradation}} \right) \times 100
\]

Results

Figure 1. Adsorption of meropenem onto AN 69 filter. Comparison with stability over 3 hours at 37°C.

Figure 2. Adsorption of 50 mg/L vaborbactam onto AN 69 filter Comparison with stability over 3 hours at 37°C.

Figure 3. The effect of point of dilution on meropenem and vaborbactam filter clearance (with ST100 filter) at different effluent and blood flow rates.

Table 1. The effect of point of dilution on meropenem/vaborbactam sieving coefficients of AN69 ST100 filter at different blood and effluent flow rate.

<table>
<thead>
<tr>
<th>Blood Flow Rate (mL/min)</th>
<th>Effluent Flow Rate (L/h)</th>
<th>Meropenem</th>
<th>Vaborbactam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-filter</td>
<td>Post-filter</td>
<td>Pre-filter</td>
</tr>
<tr>
<td>200</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1.05 ± 0.09</td>
<td>1.08 ± 0.17</td>
<td>0.78 ± 0.10</td>
</tr>
<tr>
<td>100</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1.14 ± 0.12</td>
<td>1.07 ± 0.02</td>
<td>0.88 ± 0.15</td>
</tr>
<tr>
<td></td>
<td>1.10 ± 0.06</td>
<td>1.09 ± 0.09</td>
<td>0.90 ± 0.14</td>
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<tr>
<td></td>
<td>1.06 ± 0.16</td>
<td>0.97 ± 0.16</td>
<td>0.64 ± 0.39</td>
</tr>
<tr>
<td></td>
<td>1.01 ± 0.13</td>
<td>1.08 ± 0.14</td>
<td>0.79 ± 0.16</td>
</tr>
<tr>
<td></td>
<td>1.02 ± 0.12</td>
<td>1.02 ± 0.08</td>
<td>0.80 ± 0.14</td>
</tr>
</tbody>
</table>

Conclusions

• No loss of vaborbactam dose due to adsorption compared with minimal loss of meropenem
• Effluent flow rate appears the most important factor affecting meropenem/vaborbactam clearance
• Post filter dilution is associated with increased clearance particularly at high effluent flow rate
• Dosing according to existing meropenem data in CVVH is likely to be sufficient

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