VNRX-5133, a novel broad-spectrum β-lactamase inhibitor, enhances the activity of cefepime against Enterobacteriaceae and P. aeruginosa isolates in a neutropenic mouse-thigh infection model

Background

VNRX-5133 is a new β-lactamase inhibitor with direct inhibitory activity against Ambler Class A (ESBL and KPC), B (NDM and VIM), C (AmpC) and D β-lactamases. In the present study the efficacy of VNRX-5133 in rescuing cefepime against highly resistant gram (-) bacteria was assessed in a neutropenic mouse thigh infection model.

Methods

CD1 neutropenic mice were infected intramuscularly with 10^6–10^7 CFU. Strains used were 4 E. coli, 3 K. pneumoniae and 2 P. aeruginosa with different resistance mechanisms (VIM, KPC, TEM, SHV-1, OXA-1, CTX-M, AmpC, OmpK35red) and cefepime MICs of 8-256 mg/L. Two hours after infection, cefepime (8-128 mg/kg) was given alone every 2h and suboptimal cefepime doses were combined with VNRX-5133 (0.03-128 mg/kg) every 2, 4 and 8h for 24h. CFU/thigh was determined by quantitative culture. Cefepime and VNRX-5133 concentrations were measured in serum with LC/MS-MS and free drug concentrations were estimated based on 20% protein binding for both drugs. The % time unbound concentrations remained above MIC (%fT>MIC) and a threshold concentration (%fT>CT) required for stasis and 1log kill were calculated for each strain.

Results

A two-compartment model best described the pharmacokinetics of cefepime and VNRX-5133. The static daily dose of cefepime was 48.0-2192.9 mg/kg. Cefepime alone was not active at 4-8 mg/kg q2h but stasis and 1log kill were restored when combined with VNRX-5133. The q2h regimen was more effective than q4h and q8h VNRX-5133 regimens. The %fT>CT best described VNRX-5133 efficacy. %fT>CT values based on q2h regimens for Enterobacteriaceae and P. aeruginosa are shown below.

<table>
<thead>
<tr>
<th>Strain</th>
<th>%fT&gt;CT</th>
<th>C_0 (mg/L)</th>
<th>Stasis</th>
<th>1 log kill</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td></td>
<td>0.063</td>
<td>&lt;56.6</td>
<td>&lt;57.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0</td>
<td>10.4</td>
<td>&lt;26.6</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td></td>
<td>1.0</td>
<td>43.3</td>
<td>74.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.0</td>
<td>21.9</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Conclusions

VNRX-5133 by inhibiting a broad spectrum of serine and metallo β-lactamases, restored the in vivo activity of cefepime against highly resistance gram (-) bacteria. The %fT>CT best described VNRX-5133 efficacy, with Enterobacteriaceae strains requiring lower VNRX-5133 exposures than P. aeruginosa for the same effect. These results may serve to guide selection of dosing regimens in humans.

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