Efficacy of cefepime / VNRX-5133, a novel broad-spectrum β-lactamase inhibitor (BS-BLI), in a murine bacteremia infection model with carbapenem-resistant Enterobacteriaceae (CREs)

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Background

Existing β-lactamase inhibitors are not effective against all the emergent extended spectrum β-lactamases (ESBLs) and carbapenem-hydrolyzing β-lactamases, including the metallo enzymes. The current study was performed to determine the *in vivo* efficacy of cefepime (FEP) in combination with a novel broad-spectrum potent and selective direct β-lactamase inhibitor in a murine bacteremia model against carbapenem resistant *E. coli* and *K. pneumoniae* isolates.

Methods

The *in vitro* MIC values of selected compounds were determined by broth microdilution methods against a panel of Gram-negative bacteria in accordance with CLSI guidelines. *In vivo* studies utilized mice that were challenged by intraperitoneal injection of a defined inoculum of *E. coli* (NDM-1) or *K. pneumoniae* (KPC-2, VIM-4, CMY-4), resulting in a lethal systemic infection within 24-36 hours. Doses of FEP alone or in a 2:1 ratio with VNRX-5133 or tazobactam (Tzb) were administered subcutaneously at 1 hr post-infection. A census of survivors was recorded over 6 days and the median effective dose (ED_{50}) for each treatment was calculated using Probit analysis.

Results

The ED_{50} for FEP alone against the *E. coli* (NDM-1 producer) infection was 15.4 mg/kg and was was reduced to 3.3 mg/kg when combined at 2:1 with VNRX-5133 and 17.9 mg/kg when combined with Tzb. Against the *K. pneumoniae* (KPC-2, VIM-4, CMY-4 producer) infection, the ED_{50} of 4.6 mg/kg for FEP alone was reduced to 0.99 mg/kg for FEP/VNRX-5133 while remaining at 5.8 mg/kg for FEP/Tzb. In each of these infection models, the addition of VNRX-5133 reduced the FEP ED_{50} by approximately 5-fold, while the FEP ED_{50} remained relatively unchanged when combined with Tzb.

Conclusions

Administration of VNRX-5133 was shown to enhance the efficacy of cefepime for the treatment of systemic infections with CRE strains producing multiple enzymes including NDM-1, KPC-2 and VIM-4. VNRX-5133 was more effective than tazobactam in restoring cefepime efficacy and warrants further studies to explore the clinical therapeutic utility of this novel broad-spectrum selective and direct β-lactamase inhibitor.

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