In vitro activity of cefepime alone and in combination with the broad-spectrum β-lactamase inhibitor VNRX-5133 against ESBL and carbapenamases harbouring Enterobacteriaceae and *Pseudomonas spp*

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Background

Extended spectrum β-lactamase (ESBL) and carbapenemase producing strains are increasing worldwide. VNRX-5133 is a newly developed broad-spectrum beta-lactamase inhibitor with potent and direct inhibitory activity against Ambler Class A (ESBL and KPC), B (NDM and VIM), C (AmpC) and D β-lactamases. To evaluate the potential clinical feasibility and concentrations to be used in MIC determinations in the clinical laboratory, we studied the inhibition of clinically and molecularly well-documented ESBL and carbapenemase producing strains.

Methods

Clinically and molecularly well-documented ESBL and carbapenemase producing strains (42 *Escherichia coli*, 39 *Klebsiella pneumoniae*, 29 *Pseudomonas aeruginosa*, 16 *Enterobacter cloacae*, 2 *Citrobacter freundii*, 2 *Enterobacter aerogenes*) with a variety of resistance mechanisms were used. MICs were determined and evaluated following EUCAST and ISO compliant methods. Full checkerboard experiments were performed to study interactions with two-fold dilutions over the range of 0.063-256 mg/L FEP and 0.032-32 mg/L VNRX-5133 in duplicate.

Results

The MIC_{50} and MIC_{90} of cefepime for all Enterobacteriaceae isolates (n=101) were 32 and 256 mg/L, respectively. For *P. aeruginosa* isolates this was 32 and 128 mg/L, respectively. The 50th and 90th percentile concentration of VNRX-5133 required to reduce the MIC of cefepime to 8 mg/L (the current clinical breakpoint of cefepime high dose) for all Enterobacteriaceae isolates was <0.031/0.5 mg/L, while for *P. aeruginosa* isolates this was 1 and 32 mg/L. At a fixed concentration of 1 mg/L VNRX-5133, the MIC_{50} and MIC_{90} were reduced to 0.25 and 2 mg/L, respectively, for Enterobacteriaceae isolates, and to 16 and 64 mg/L, respectively, for *P. aeruginosa* isolates. To obtain a breakpoint MIC of ≤16 mg/L cefepime for 90% of the *P. aeruginosa* isolates, including strains with reduced permeability, 4 mg/L VNRX-5133 was required.

Conclusions

Increasing concentrations of VNRX-5133 resulted in a decreasing MIC of cefepime to clinically relevant values. At a fixed concentration of 4 mg/L VRNX-5133 all Enterobacteriaceae were susceptible. The combination cefepime/VNRX-5133 is a promising alternative treatment option for infections caused by ESBL harbouring Enterobacteriaceae strains and the majority of *P. aeruginosa*.

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