Pharmacodynamics of the novel broad-spectrum β-lactamase inhibitor VNRX-5133 in combination with cefepime in neutropenic female CD-1 mice with experimental pneumonia

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Background

Although cefepime has an extended spectrum against gram(-) bacteria, it is susceptible to degradation by ESBLs and other serine- and metallo-β-lactamases. VNRX-5133 is a newly developed inhibitor which directly inhibits all four classes of β-lactamases. For optimal dosing, exploration of pharmacokinetic/pharmacodynamic relationships is required.

Methods

CD1 neutropenic mice were intranasally infected with 10^6–10^7 CFU bacteria. 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 and OmpK35red) and cefepime MICs of 8-256 mg/L. Two hours after infection, cefepime (8-128 mg/kg) was given alone every 2h for 24h and suboptimal doses were combined with VNRX-5133 (0.03-128 mg/kg) in a dose fractionation design or every 2h. CFU in lungs was determined with quantitative cultures. Cefepime and VNRX-5133 concentrations were measured in serum with LC/MS-MS. Free drug concentrations were estimated based on 20% protein binding for both drugs. The efficacy of VNRX-5133 administered every 2h and 8h was compared. The % of time the unbound concentrations remained above MIC (%*f*T>MIC) and a threshold concentration (%*f*T>C_T) associated with stasis and 1logkill were calculated for each strain.

Results

A two-compartment model best described the pharmacokinetics of cefepime and VNRX-5133. Although high doses were required, the static %*f*T>MIC of cefepime during monotherapy was 0% for all strains, indicating that the MIC overestimates resistance *in vivo*. Cefepime doses of 2 mg/kg q2h, resulting in a %*f*T>MIC of 57.7% for a cefepime MIC of 0.125 mg/L (the ECOFF for most Enterobacteriaceae) were not effective. The activity of cefepime was restored by VRNX-5133. The q2h regimens were more effective than q8h VNRX-5133 regimens. The %*f*T>C_T best described VNRX-5133 efficacy. %*f*T>C_T values based on q2h regimens for Enterobacteriaceae and *P. aeruginosa* are shown below.

	%*f*T>C_T		
	C_T (mg/L)	**Stasis**	**1 log kill**
Enterobacteriaceae	0.125	34.8	62.2
	0.25	21.4	45.2
P. aeruginosa	1.0	75.2	100
	4.0	39.6	59.5

Conclusions

VNRX-5133 demonstrated time-dependent activity in restoring the activity of cefepime against highly resistant serine- and metallo-β-lactamase producers when a certain %*f*T>C_T was achieved. These results can be used for optimal design of dosing regimens in humans.

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