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

ECCMID 2018 | Paper Poster Session #76 | Paper Poster #P1540 | April 23, 2018 | 12:30pm – 13:30pm | Paper Poster Arena

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 10^6–10^7CFU. 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 (%*f*T>MIC) and a threshold concentration (%*f*T>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 %*f*T>CT best described VNRX-5133 efficacy. %*f*T>CT 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	0.063	<56.6	<57.6
	1.0	10.4	<26.6
P. aeruginosa	1.0	43.3	74.3
	4.0	21.9	N/A

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 %*f*T>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.

Authors

Panagiota-Christina Georgiou[1]

Maria Siopi[1]

Marilena Tsala[1]

Claudia Lagarde[2,3]

Wendy Kloezen[3]

Ria Donnelly[2,3]

Joseph Meletiadis[1,3]

Johan W. Mouton[3]

Affiliation

[1] Clinical Microbiology Laboratory, Attikon Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

[2] Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, The Netherlands

[3] Department of Medical Microbiology and Infectious Diseases, Erasmus Medical Center, Rotterdam, The Netherlands

This project has been funded in whole or in part with Federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN272201300019C, and Wellcome Trust under Award No. 360G-Wellcome-101999/Z/13/Z.