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Rescue of Ceftibuten Activity by the Oral β-Lactamase Inhibitor VNRX-7145 against Enterobacteriaceae Expressing Class A, C and/or D β-Lactamases

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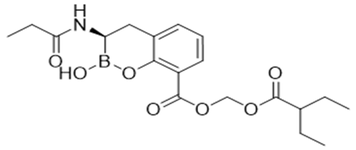
Background

VNRX-7145 is a novel, orally bioavailable, cyclic boronate β-lactamase inhibitor (BLI). In vivo, VNRX-7145 undergoes biotransformation to the active BLI, VNRX-5236, that covalently and reversibly binds the active site serine of Ambler Class A, C and D β-lactamases[1]. The only clinically-available oral BLI, clavulanic acid (CLA), is active against some Class A extended spectrum β-lactamases (ESBLs) but has little to no activity against Class C cephalosporinases or carbapenem-hydrolyzing enzymes (e.g., KPC and OXA-48)[2]. VNRX-5236 in combination with the oral β-lactam ceftibuten has antibacterial activity against strains of Enterobacteriaceae expressing Ambler Class A, C and/or D enzymes[3]. Here, the concentrations of VNRX-5236 and CLA necessary to potentiate the activity of ceftibuten in these strains were compared.

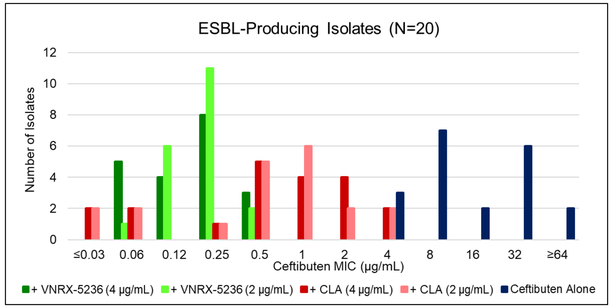
Structure of VNRX-7145

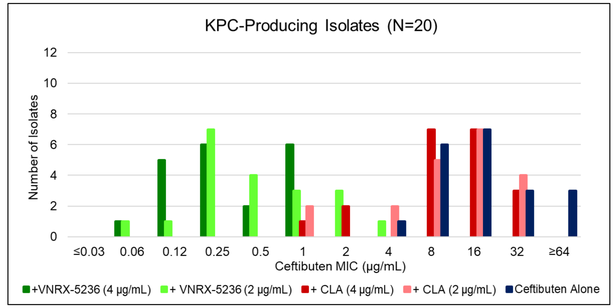


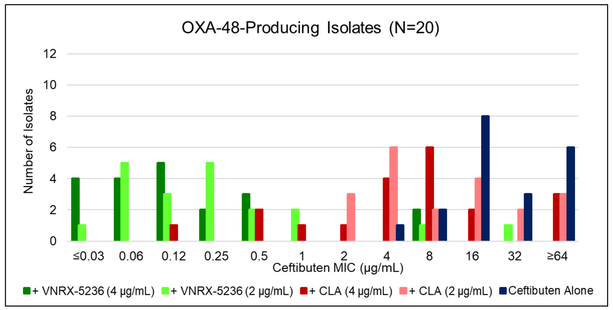
Methods

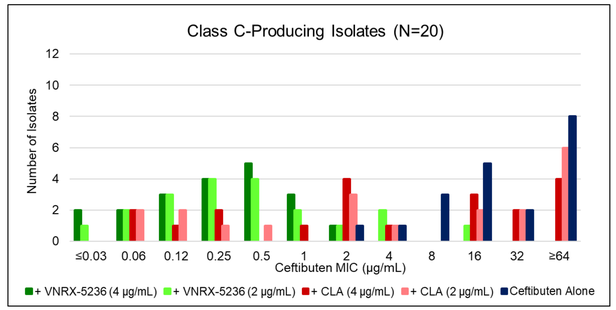
Minimum inhibitory concentrations (MICs) were determined by broth microdilution following CLSI methods[4,5]. The test set of strains had elevated ceftibuten MICs (2 µg/mL - ≥64 µg/mL) and consisted of Enterobacteriaceae expressing ESBLs (n=20), KPCs (n=20), Class C (n=20) and/or OXA-48 (n=20) β-lactamases. For each isolate, one microtiter plate was prepared and formatted as a checkerboard with the BLI (VNRX-5236 or CLA) titrated down the plate and ceftibuten titrated across the plate. Each agent was also tested alone. MICs were read as the well with the lowest concentration of ceftibuten with no visible growth at each concentration of BLI.

Ceftibuten MIC Distributions by Enzyme Subset

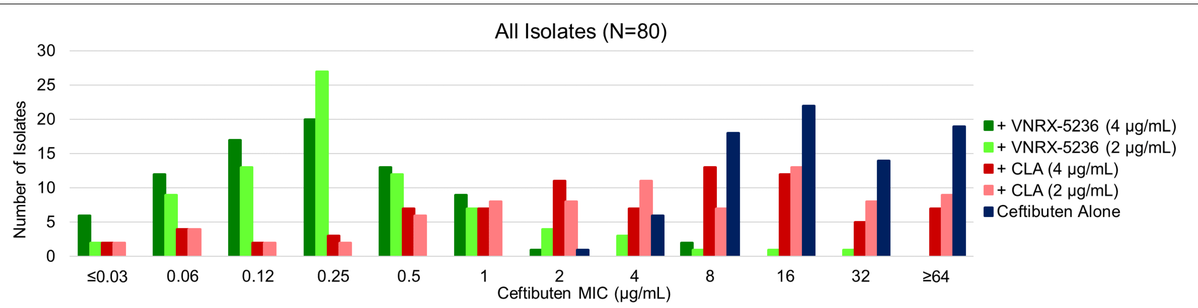








Ceftibuten MIC Distribution for All Isolates



MIC Summary Table by Enzyme Subset

Concentrations of BLI (µg/mL) required to reduce ceftibuten MIC to 1, 2, 4, 8, 16 µg/mL in 90% of strains by enzyme subtype. Ceftibuten alone MIC_{90} ≥ 32 µg/mL in all enzyme subsets.

Enzyme Subset (N=20 each)	Ceftibuten Concentration (µg/mL)									
	1		2		4		8		16	
	VNRX-5236	CLA	VNRX-5236	CLA	VNRX-5236	CLA	VNRX-5236	CLA	VNRX-5236	CLA
ESBL	0.25	≥8	0.12	2	≤0.06	0.25	≤0.06	0.12	≤0.06	≤0.06
KPC	4	≥16	2	≥16	1	≥16	1	≥16	0.5	≥16
OXA-48	2	≥16	1	≥16	1	≥16	0.5	≥16	0.25	≥16
Class C	4	≥16	4	≥16	1	≥16	0.5	≥16	0.25	≥16
All Isolates	4	≥8	2	≥8	1	≥8	0.5	≥8	≤0.12	≥8

Conclusions

- VNRX-5236 was more potent than CLA against ESBL-expressing isolates and, unlike CLA, has a spectrum of activity that encompasses enzymes of the KPC, Class C and OXA-48 subtypes.
- The ceftibuten/VNRX-7145 combination has the potential to be an important new orally bioavailable option against resistant Enterobacteriaceae infections.

References

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