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The Orally Bioavailable β-lactamase Inhibitor VNRX-7145 Restores Bactericidal Activity of Ceftibuten Against Enterobacteriaceae Expressing Ambler Class A, C and D Enzymes

Jodie C. Hamrick, Cassandra L. Chatwin, Kaitlyn J. John, Greg Moeck, Luigi Xerri, and Daniel C. Pevear

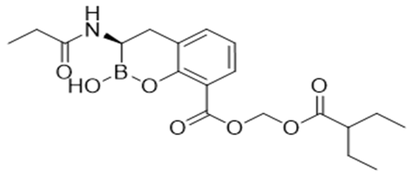
VenatoRx Pharmaceuticals, Inc. Malvern, PA 19355 USA.

VenatoRx Pharmaceuticals
610.644.8935
hamrick@venatorx.com

Background

VNRX-7145 is a novel, orally bioavailable, cyclic boronate-based β-lactamase inhibitor (BLI) that undergoes biotransformation to the active BLI VNRX-5236 *in vivo*. VNRX-5236 has potent and selective direct inhibitory activity against Ambler class A, C and D enzymes including those that hydrolyze carbapenems. 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) creating a need for new oral inhibitors with advanced spectrum. In this study, time-kill kinetics were used to assess the ability of VNRX-5236 to rescue the bactericidal activity of ceftibuten against Enterobacteriaceae isolates expressing Class A, C, and D enzymes.

Structure of VNRX-7145



Methods

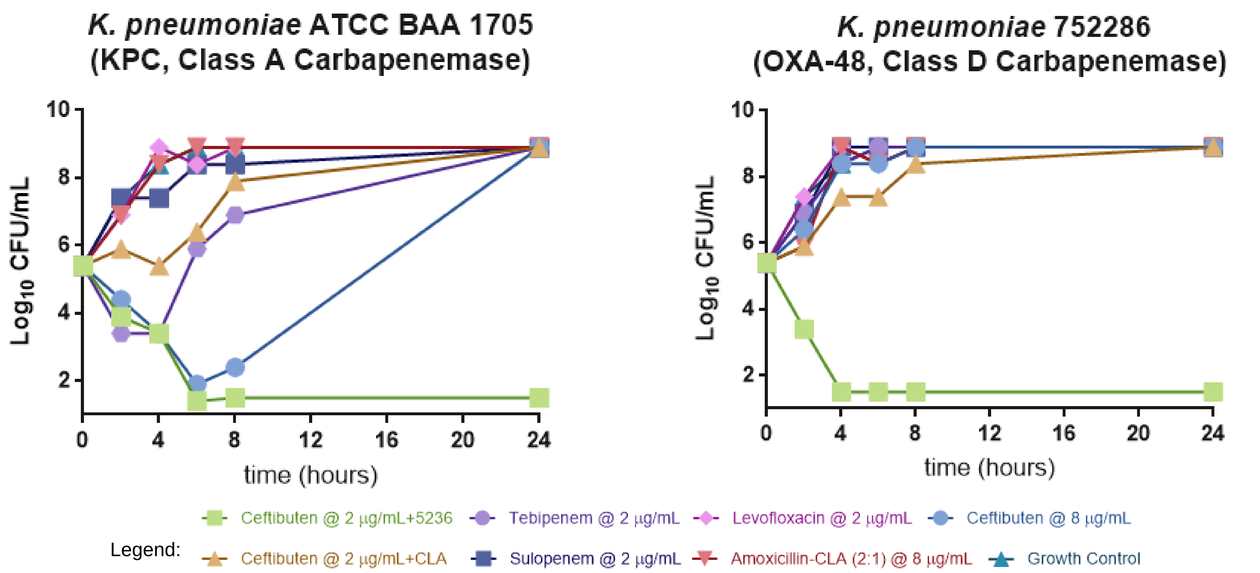
Minimal bactericidal Concentrations (MBCs) were determined using time-kill experiments conducted following modified NCCLS 1999 methods utilizing deep-well plates. Antibacterial agents were tested in 2-fold dilutions from 0.06 to 32 µg/mL. VNRX-5236 and CLA were fixed at 4 µg/mL in combination with ceftibuten. Viable counts were determined at 0, 2, 4, 6, 8 and 24 hours and kill curves generated by plotting Log_{10} CFU/mL versus time. Tests were conducted in 4 ceftibuten-resistant clinical isolates of Enterobacteriaceae expressing β-lactamases. The presence of β-lactamase genes was verified by PCR with expression determined phenotypically. Bactericidal activity was defined as ≥3-log_{10} killing vs starting inoculum.

Summary of Bactericidal Activity for Each Antibacterial Agent Tested

	K. pneumonaie ATCC BAA 1705 (KPC)		*E. coli* ESBL 4 (CTX-M-15)		*E. cloacae* ECLO1 (p99)		*K. pneumoniae* 752286 (OXA-48)	
	MIC (µg/mL)	MBC (µg/mL)	MIC (µg/mL)	MBC (µg/mL)	MIC (µg/mL)	MBC (µg/mL)	MIC (µg/mL)	MBC (µg/mL)
Ceftibuten	16	16	32	>32	64	>32	128	>32
Ceftibuten/clavulanic Acid	8	16	0.12	1	≥256	>32	16	16
Ceftibuten/VNRX-5236	0.12	0.25	0.12	0.12	0.25	1	0.25	0.25
Sulopenem	32	32	0.12	0.12	1	1	16	>32
Tebipenem	32	32	≤0.06	0.06	0.25	0.25	16	>32
Levofloxacin	64	>32	32	32	0.12	0.12	32	>32
Amoxicillin-Clavulanic Acid (2:1)	≥256	>32	16	16	128	>32	≥256	>32

MIC results were determined following CLSI M07 Ed 11 (2018) methods and interpreted according to CLSI M100 Ed. 29 (2019). MBC values were determined by time-kill as the lowest concentration to maintain bactericidal activity at 24 hours. Red text notes an MIC considered to be non-susceptible for those antibacterial agents with established CLSI breakpoints

Time-kill Curves in Enterobacteriaceae Expressing Serine β-lactamase



Summary of Results

- The time-kill curves show data at the breakpoint for approved agents and at 2 µg/mL for all investigational agents.
- All four β-lactamase-expressing strains were non-susceptible to amoxicillin-clavulanic acid (MIC ≥16 µg/mL) and ceftibuten alone (MIC ≥16 µg/mL).
- VNRX-5236 restored bactericidal activity of ceftibuten in all 4 strains reaching 2- to 4-log_{10} CFU/mL killing by 8 hours and maintaining ≥4-log_{10} CFU/mL killing without regrowth through 24 h at 1x to 2x the MIC. Ceftibuten/VNRX-5236 was the only agent tested to do so in all strains including those producing carbapenemase enzymes that hydrolyzed the oral penems (e.g., Tebipenem and Sulopenem).
- VNRX-5236 alone was tested and was found to have no intrinsic antibacterial activity.

Conclusions

VNRX-5236 restored the bactericidal activity of ceftibuten to near wild-type levels against cephalosporin-resistant and carbapenem-resistant Enterobacteriaceae. Ceftibuten/VNRX-7145 may provide a potent oral treatment option for hospital- and community-acquired infections caused by β-lactamase-expressing Enterobacteriaceae for which there are currently few treatment options available.

References

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