Assessment of activity of a novel orally bioavailable β-lactam/β-lactamase inhibitor combination, ceftibuten/VNRX-7145 (VNRX-5236 etzadroxil) against Enterobacterales carrying *bla*$_{OXA-48}$

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Abstract

Background: Most expanded-spectrum β-lactam/β-lactamase inhibitor combinations (e.g., ceftazidime-avibactam) are only available in an intravenous formulation. VNRX-7145 (VNRX-5236 etzadroxil) is a novel, orally bioavailable boronic acid β-lactamase inhibitor prodrug that can be metabolized to release the active beta-lactamase inhibitor, VNRX-5236, which inhibits class A, C, and D β-lactamases. VNRX-5236 is being developed in combination with the oral cephalosporin, ceftibuten, to address the unmet need for oral agents active against resistant Enterobacterales. Herein, we examined the *in vitro* activity of ceftibuten/VNRX-5236 vs. other orally bioavailable agents against a diverse panel of Enterobacterales carrying *bla*$_{OXA-48}$, an Ambler class D carbapenemase.
Methods: CLSI-based agar dilution susceptibility testing was conducted using ceftibuten/VNRX-5236 (with VNRX-5236 fixed at 4 mg/L) and comparators ceftibuten, tebipenem, sulopenem, ceftibuten-clavulanic acid, amoxicillin-clavulanic acid, and levofloxacin. Enterobacterales producing OXA-48 included *Escherichia coli*, *Escherichia hermannii*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*. Strains (N=50) were obtained from several different geographical locations including France, Lebanon, Morocco, Algeria, Switzerland, Sultanate of Oman, Egypt, Libya, the Netherlands, and Turkey between 2007-2012 and were isolated from human sputum, urine, rectal swabs, pus, blood, placenta, and bronchoalveolar lavage fluid.
Results: The ceftibuten/VNRX-5236 combination demonstrated potent activity, decreasing the MIC$_{90}$ for ceftibuten alone from >32 µg/mL to 0.5 µg/mL. Of the orally bioavailable antibiotics tested, the rank order of potency by MIC$_{90}$ value against these Enterobacterales isolates carrying *bla*$_{OXA-48}$ was ceftibuten/VNRX-5236 (susceptible (S), 96%) > ceftibuten-clavulanic acid (S, 38%) > levofloxacin (S, 34%) = tebipenem > sulopenem > ceftibuten (S, 26%) > amoxicillin-clavulanic acid (S, 0%).
Conclusions: Ceftibuten/VNRX-5236 demonstrated greater activity than the other tested orally bioavailable comparators against this panel of highly drug-resistant Enterobacterales. This study supports further development of this combination to address unmet needs for patients infected by such challenging pathogens.

Background

- Carbapenemase-producing Enterobacterales (CPE) are an urgent threat to public health [1].
- A strategy to combat CPE is the use of β-lactam/β-lactamase inhibitor combinations.
- Currently, the FDA-approved β-lactam/β-lactamase inhibitor combinations (i.e., ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam) are only available for intravenous infusion.
- VNRX-7145 is a novel, investigational boronic acid β-lactamase inhibitor that is metabolically converted to the active form, VNRX-5236, when administered orally and is in development partnered with ceftibuten [2].

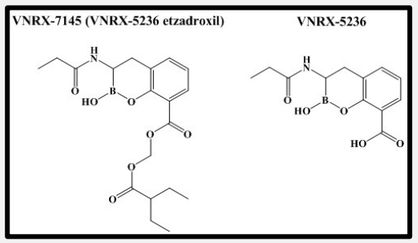

Figure 1. Chemical structure of VNRX-7145 (VNRX-5236 etzadroxil) (left), the prodrug of VNRX-5236 (right).

Goal: Evaluate the antimicrobial activity of ceftibuten/VNRX-5236 against a panel of 50 CPE carrying *bla*$_{OXA-48}$.

Results

Table 1. Agar dilution susceptibility testing results comparing various orally bioavailable agents. The table shows the number of isolates that had each of the indicated MIC value for each drug. CTB/VNRX-5236 was the most active agent against these CPE carrying *bla*$_{OXA-48}$, with 96% susceptible to the combination and the lowest MIC$_{50}$ /MIC$_{90}$ values (0.125/0.5 µg/mL respectively). EUCAST breakpoints for CTB (S ≤ 1 µg/mL; R ≥ 2 µg/mL) were used to provisionally assign phenotypes to the combinations with VNRX-5236 and CLA. CLSI breakpoints were used for the other combinations and are as follows: AMC (S ≤ 8/4 µg/mL; I = 16/8 µg/mL; R ≥ 32/16 µg/mL), and LVX (S ≤ 0.5 µg/mL; I = 1 µg/mL; R ≥ 2 µg/mL). Breakpoints are not available for TEB and SUL. (CTB = ceftibuten, TEB = tebipenem, SUL = sulopenem, CLA = clavulanic acid, AMC = amoxicillin-clavulanic acid, LVX = levofloxacin. % S = percent susceptible, % I = percent intermediate, % R = percent resistant. NT = not tested, NA = not available, - = not applicable.)

	Number of Isolates						
MIC (µg/mL)	**CTB**	**CTB/ VNRX-5236**	**TEB**	**SUL**	**CTB-CLA**	**AMC**	**LVX**
≤ 0.03	NT	NT	0	0	NT	NT	4
0.06	5	22	0	0	3	NT	6
0.125	4	14	3	0	4	0	2
0.25	1	6	7	0	3	0	1
0.5	3	4	13	0	4	0	4
1	0	2	14	9	5	0	3
2	3	1	4	12	12	0	0
4	4	0	2	19	8	0	2
>4	-	-	7	-	-	-	28
8	7	0	NT	3	3	0	NT
>8	-	-	-	7	-	-	-
16	11	0	NT	NT	2	0	NT
32	3	1	NT	NT	3	0	NT
>32	9	0	-	-	-	-	-
64	NT	NT	NT	NT	0	0	NT
>64	-	-	-	-	3	-	-
128	NT	NT	NT	NT	NT	5	NT
>128	-	-	-	-	-	45	-
MIC$_{50}$	8	0.125	1	4	2/1	>128/64	>4
MIC$_{90}$	>32	0.5	>4	>8	32/16	>128/64	>4
% S	26	96	NA	NA	38	0	34
% I	NA	NA	NA	NA	4	0	6
% R	74	4	NA	NA	62	100	60

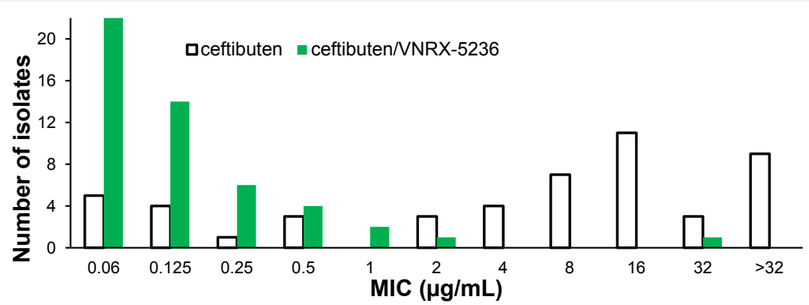

Figure 2. Agar dilution susceptibility testing results of ceftibuten alone (white bars) compared to ceftibuten combined with VNRX-5236 (green bars) tested against a panel of 50 CPE carrying *bla*$_{OXA-48}$. The addition of VNRX-5236 to ceftibuten reduced the MIC$_{90}$ values from >32 µg/mL to 0.5 µg/mL.

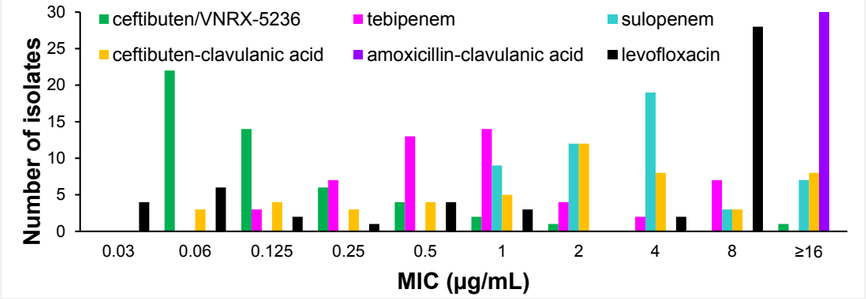

Figure 3. Agar dilution susceptibility testing results comparing ceftibuten/VNRX-5236 (dark blue bars), to other orally bioavailable agents, tebipenem (pink bars), sulopenem (turquoise bars), ceftibuten-clavulanic acid (orange bars), amoxicillin-clavulanic acid (purple bars), and levofloxacin (black bars) against 50 CPE carrying *bla*$_{OX-48}$.

Conclusions

- Our current arsenal to combat CPE does not include an effective orally-administered β-lactam or β-lactam/β-lactamase inhibitor combination.
- The ceftibuten/VNRX-5236 combination displayed the lowest overall MIC$_{50}$/MIC$_{90}$ compared to other orally available agents against the CPE evaluated in this study.
- The addition of an oral β-lactam/β-lactamase inhibitor combination to our arsenal would address a significant unmet need in the treatment of CPE, which would result in decreased hospital stays and expense.

References

1. CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services.
2. Chatwin CL, et. al. *Microbiological characterization of VNRX-5236: a broad spectrum β-lactamase inhibitor for rescue of the orally bioavailable cephalosporin ceftibuten as a carbapenem-sparing agent against strains of Enterobacterales expressing extended spectrum β-lactamases and serine carbapenemases.* Antimicrob Agents Chemother. 2021 May 17 PMID: 34001510.

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