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Antimicrobial Activities of Cefepime, Meropenem, Aztreonam, and Piperacillin Combined with Nacubactam against Molecularly Characterized *Enterobacterales* Collected Worldwide

Helio S. Sader[1], Timothy Doyle[1], Kenichiro Kondo[2], Yu Nagira[2], Mariana Castanheira[1]

[1] JMI Laboratories, North Liberty, Iowa, USA; [2] Meiji Seika Pharma Co., Ltd., Tokyo, Japan

Introduction

- Nacubactam (OP0595) is a novel non-β-lactam diazabicyclooctane β-lactamase inhibitor under development for the treatment of serious Gram-negative infections.
- Compared to avibactam, nacubactam has an additional aminoethoxy group attached to the carbamoyl side chain that is responsible for its significant, intrinsic antimicrobial activity.
- We evaluated the *in vitro* activities of various nacubactam combinations against well-characterized *Enterobacterales* subsets producing clinically relevant β-lactamases.

Materials and Methods

Bacterial isolates

- A total of 571 molecularly- and/or phenotypically-characterized clinical bacterial isolates were collected from 137 medical centers located in 42 countries.
- Isolates were selected from the SENTRY collection based on whole genome sequencing (85%) or PCR plus sequencing (15%) results, except for in the case of isolates from the stably derepressed AmpC group, which were selected based on species identification and resistance phenotype.
- These isolates were collected from patients with pneumonia (168 isolates; 29.4%), bloodstream infections (162; 28.4%), complicated urinary tract infections (99; 17.3%), skin and soft tissue infections (91; 15.9%), intra-abdominal infections (40; 7.0%), and other infection types (11; 1.9%).
- Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the program.

Susceptibility testing

- The broth microdilution test method was conducted according to CLSI specifications.
- Nacubactam combinations were tested at a 1:1 ratio.
- CLSI and EUCAST susceptibility interpretive criteria were applied for comparator agents.

Results

- Based on $MIC_{50/90}$ and percentage inhibited at the breakpoint for the β-lactam tested alone, the most active nacubactam combination against the overall collection was aztreonam-nacubactam ($MIC_{50/90}$, 1/2 mg/L; 100.0% inhibited at ≤4 mg/L), followed by piperacillin-nacubactam ($MIC_{50/90}$, 1/4 mg/L; 97.2% inhibited at ≤16 mg/L), cefepime-nacubactam ($MIC_{50/90}$, 1/2 mg/L; 93.5% inhibited at ≤2 mg/L), and meropenem-nacubactam ($MIC_{50/90}$, 0.5/4 mg/L; 76.7% inhibited at ≤1 mg/L). See Tables 1 and 2 and Figure 1.
- All nacubactam combinations were highly active against KPC producers (Table 2 and Figure 2).
- All nacubactam combinations, except meropenem-nacubactam, were very active against OXA-48-like producers (Table 2 and Figure 3).
- Aztreonam-nacubactam was the most active nacubactam combination against metallo-β-lactamase (MBL) producers and carbapenemase co-producers (isolates producing ≥2 carbapenemases). See Table 2 and Figures 4 and 5.
- All nacubactam combinations were highly active (100.0% inhibited at the β-lactam breakpoint) against isolates producing extended-spectrum β-lactamases (ESBLs), stably derepressed AmpCs, and plasmidic AmpC β-lactamases (Table 2).
- Ceftazidime-avibactam (fixed 4 mg/L) and meropenem-vaborbactam (fixed 8 mg/L) were active against 99.1% and 41.1% of OXA-48-like producers, respectively (data not shown).
- Ceftazidime-avibactam (fixed 4 mg/L) and meropenem-vaborbactam (fixed 8 mg/L) exhibited limited activity against MBL-producers and carbapenemase co-producers (<20.0%S per CLSI; data not shown).
- Regional differences in the *in vitro* activities of the antimicrobial agents tested were noted and may reflect geographic variabilities in the distribution of resistance mechanisms.

Conclusions

- The potent activity and broad antibacterial spectrum of the nacubactam combinations against the Gram-negative organisms evaluated in the present study indicate that nacubactam represents a valuable β-lactamase inhibitor when combined with cefepime, aztreonam, meropenem, or piperacillin.
- Any of these nacubactam combinations represent a valuable option for treating Gram-negative infections producing most clinically relevant β-lactamases.
- Aztreonam-nacubactam showed the greatest activity against isolate subsets that produced a MBL or co-produced carbapenemases.

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Figure 1. Antimicrobial activities of nacubactam combinations tested against 571 well-characterized *Enterobacterales* isolates collected worldwide

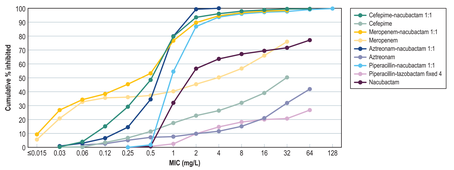

Figure 2. Antimicrobial activities of nacubactam combinations tested against 105 KPC-producing *Enterobacterales* isolates collected worldwide

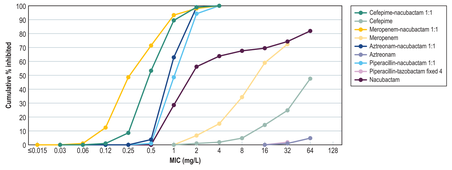

Figure 3. Antimicrobial activities of nacubactam combinations tested against 107 OXA-48-like-producing *Enterobacterales* isolates collected worldwide

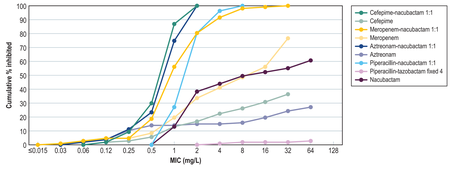

Figure 4. Antimicrobial activities of nacubactam combinations tested against 107 MBL-producing *Enterobacterales* isolates collected worldwide

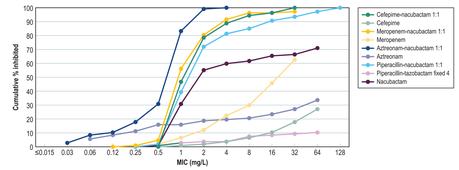

Figure 5. Antimicrobial activities of nacubactam combinations tested against 49 carbapenemase co-producer *Enterobacterales* isolates collected worldwide

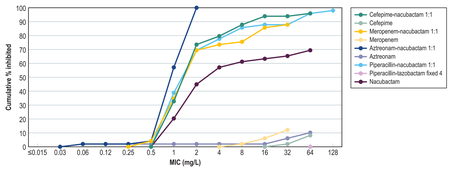

Table 1. Antimicrobial activities of nacubactam combinations and comparator agents tested against 571 well-characterized *Enterobacterales* isolates collected worldwide

Antimicrobial agent	mg/L		CLSI[a]			EUCAST[a]		
	MIC_{50}	MIC_{90}	%S	%I	%R	%S	%I	%R
Cefepime	64	>64	17.5 [b]	8.9	73.6	11.4	11.4	77.2
Cefepime-nacubactam (1:1)	1	2	[93.5][b]	[4.4][b]	[2.1][b]			
Meropenem	4	>32	40.3	5.1	54.6	45.4	11.4	43.3
Meropenem-nacubactam (1:1)	0.5	4	[76.7][b]	[13.0][b]	[10.3][b]			
Meropenem-vaborbactam (fixed 8)	0.25	>32	66.0	2.8	31.2	68.8		31.2
Aztreonam	>64	>64	11.6	3.5	84.9	7.7	3.9	88.4
Aztreonam-nacubactam (1:1)	1	2	[100.0][b]	[0.0][b]	[0.0][b]			
Piperacillin	>128	>128	0.9	3.7	95.4	0.7		99.3
Piperacillin-tazobactam (fixed 4)	>64	>64	20.0	6.8	73.2	18.2		81.8
Piperacillin-nacubactam (1:1)	1	4	[97.2][b]	[1.9][b]	[0.9][b]			
Nacubactam	2	>64						
Imipenem	4	>8	39.2	4.6	56.2	[c]		47.5
Imipenem-relebactam (fixed 4)	0.25	32	59.7	4.3	35.9	64.1		35.9
Ceftazidime	>16	>16	12.8	2.8	84.4	6.5	6.3	87.2
Ceftazidime-avibactam (fixed 4)	1	>32	73.9		26.1	73.9		26.1
Ceftolozane-tazobactam (fixed 4)	>16	>16	22.8	4.0	73.2	22.8		77.2
Cefiderocol	1	4	90.7 [d]	6.5	2.8	75.8		24.2

[a] Criteria as published by CLSI (2021) and EUCAST (2021).
[b] Values in brackets are based on CLSI breakpoints for the β-lactam alone (for comparison purposes).
[c] An arbitrary susceptible breakpoint of <=0.001 mg/L and/or >50 mm has been published by EUCAST indicating that susceptible should not be reported for this organism-agent combination and intermediate should be interpreted as susceptible increased exposure. Only resistant values are shown because breakpoints are different among organism species (EUCAST 2021).
[d] US FDA breakpoints were applied.
Organisms include: *Citrobacter freundii* species complex (20), *Enterobacter cloacae* (1), *E. cloacae* species complex (68), *Escherichia coli* (125), *Hafnia alvei* (2), *Klebsiella aerogenes* (28), *K. oxytoca* (11), *K. pneumoniae* (293), *Morganella morganii* (4), *Pluralibacter gergoviae* (1), *Proteus mirabilis* (4), *Providencia rettgeri* (1), *P. stuartii* (2), *Serratia marcescens* (10), and unspecieated *Raoultella* (1).

Table 2. Summary of the antimicrobial activities of nacubactam combinations against 571 well-characterized *Enterobacterales* isolates

Organism subset (no.)	$MIC_{50/90}$ in mg/L for nacubactam combinations (1:1 ratio):				Nacubactam $MIC_{50/90}$ (mg/L)
	Cefepime-nacubactam	Meropenem-nacubactam	Aztreonam-nacubactam	Piperacillin-nacubactam	
All *Enterobacterales* (571)	1/2 (93.5)[a]	0.5/4 (76.7)[a]	1/2 (100.0)[a]	1/4 (97.2)[a]	2/>64
ESBL-producers (105)	0.25/0.5 (100.0)	0.03/0.06 (100.0)	0.5/1 (100.0)	1/2 (100.0)	1/8
KPC-producers (105)	0.5/2 (99.0)	0.5/1 (93.3)	1/2 (100.0)	2/2 (100.0)	2/>64
OXA-producers (107)	1/2 (100.0)	1/4 (56.1)	1/2 (100.0)	2/4 (100.0)	16/>64
MBL-producers (107)	2/8 (78.5)	1/4 (56.1)	1/2 (100.0)	2/16 (90.7)	2/>64
Carbapenemase co-producers (49)	2/16 (73.5)	2/>32 (34.7)	1/2 (100.0)	2/64 (87.8)	4/>64
AmpC derepressed (65)	0.12/0.25 (100.0)	0.03/0.06 (100.0)	1/1 (100.0)	1/2 (100.0)	2/>64
Plasmidic AmpC-producers (33)	0.5/1 (100.0)	0.03/0.12 (100.0)	0.5/2 (100.0)	1/2 (100.0)	2/64

[a] The percentage inhibited at the CLSI breakpoint for the β-lactam alone was provided for comparison.

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Contact

Helio S. Sader, MD, PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: helio-sader@jmilabs.com

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