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A A C , M , A , C N M C Enterobacterales C

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Introduction

- Nacubactam (OP0595) is a novel non- -lactam diazabicyclooctane -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 -lactamases.

Results

- Based on $MIC_{50/90}$ and percentage inhibited at the breakpoint for the -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- -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 -lactam breakpoint) against isolates producing extended-spectrum -lactamases (ESBLs), stably derepressed AmpCs, and plasmidic AmpC -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 -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 -lactamases.
- Aztreonam-nacubactam showed the greatest activity against isolate subsets that produced a MBL or co-produced carbapenemases.

Funding

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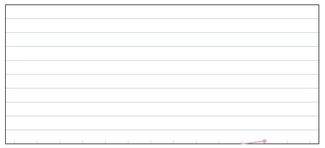
Figure 2. Antimicrobial activities of nacubactam combinations tested against 105 KPC-producing Enterobacterales isolates collected worldwide



46cam-67.79EF[7.87 Tm eona0:0DC25Tm.EF51k5 32/45.3266ji0017 2459.e491 483/0.06 (10.9) C0.393Fre471 -2.0 5/18.66 (1.9) 15439 4 7/261 -ri833C4.329 (1.0) 927 ,)43C-12.302 4 [(s96m 112.698)-15039C-1 /2634-154362-6.864Fc /1503F46cam-3.396C-0.395 /1503Fs96m -12.6 46cam

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

[a] The percentage of isolates inhibited at the breakpoint for the -lactam alone was provided in parentheses.

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