#03513Meropenem-ANT3310: a novel agent targeting serine carbapenemase-producing Enterobacterales

03. Bacterial susceptibility & resistance
03b. Resistance surveillance & epidemiology: Healthcare-associated bacteria

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Background

Carbapenemase-producing Enterobacterales (CPE) represent an increasing global public health threat, limiting available therapeutic options. Serine carbapenemases (SCP) are one of the main mechanisms driving carbapenem resistance. Current treatment protocols primarily rely on agents like ceftazidime-avibactam (CZA) and imipenem-relebactam (IMR). ANT3310, a next generation diazabicyclooctane SCP inhibitor, is being developed in combination with meropenem-MEM- for the treatment of severe infections caused by Gram-negative pathogens in hospitalized patients. This study evaluates the in vitro activity of MEM-ANT3310 against a diverse collection of SCPE clinical isolates.

Methods

Clinical isolates from a National Prevalence Survey (RECAPT-AR;181 hospitals) were analyzed. We included 407 eligible isolates with confirmed SCP production (PCR/WGS): 327 bla_{KPC}, 59 $bla_{OXA\text{-}48\text{-}like}$ (all OXA-163) and 21 bla_{KPC} plus $bla_{OXA\text{-}163}$. Species identification (MALDI-TOF) yielded (n): *K. pneumoniae* (325), *Enterobacter cloacae* (32), *Escherichia coli* (17), *Serratia marcescens* (12), and other species (21). MICs were determined by CLSI broth microdilution. ANT3310 was tested at 8 mg/L. A provisional PK/PD breakpoint of ≤8/8 mg/L defined susceptibility for MEM-ANT3310 while comparators antimicrobials were interpreted per CLSI/EUCAST breakpoints.

Results

MIC_{50} and MIC_{90} and MIC ranges for MEM-ANT3310, CZA and IMR by carbapenemase class are shown in Fig.1. At concentrations of ≤8/8 mg/L, MEM-ANT3310 inhibited 96.3 % of all SCPE (96.0% KPC; 98.3% OXA-163 and 90.5% KPC plus OXA-163). Susceptibility rates are depicted in Fig.2. MEM-ANT3310 showed statistically superior activity compared to MEM and traditional therapeutic options (fosfomycin, amikacin, tigecycline and colistin) ($p<0.0001$). No statistically significant differences were found in the performance among MEM-ANT3310, IMR, and CZA ($p>0.05$). Notably, MEM-ANT3310 remained susceptibility in all 3 isolates that were non-susceptible to IMR and/or CZA.

Conclusions

MEM-ANT3310 demonstrated excellent in vitro activity against SCPE, comparable to those of IMR and CZA. Additionally, its ability to retain activity against isolates non-susceptible to either IMR or CZA suggests a complementary role within the therapeutic armamentarium for SCP. These findings support MEM-ANT3310 as a promising candidate against SCP in high-burden settings, also in those with emerging resistance or limited access to other β-lactam/β-lactamase inhibitor combinations.

Fig.1 MEM-ANT3310, CZA and IMR: MIC_{50} , MIC_{90} and MIC ranges by carbapenemase class

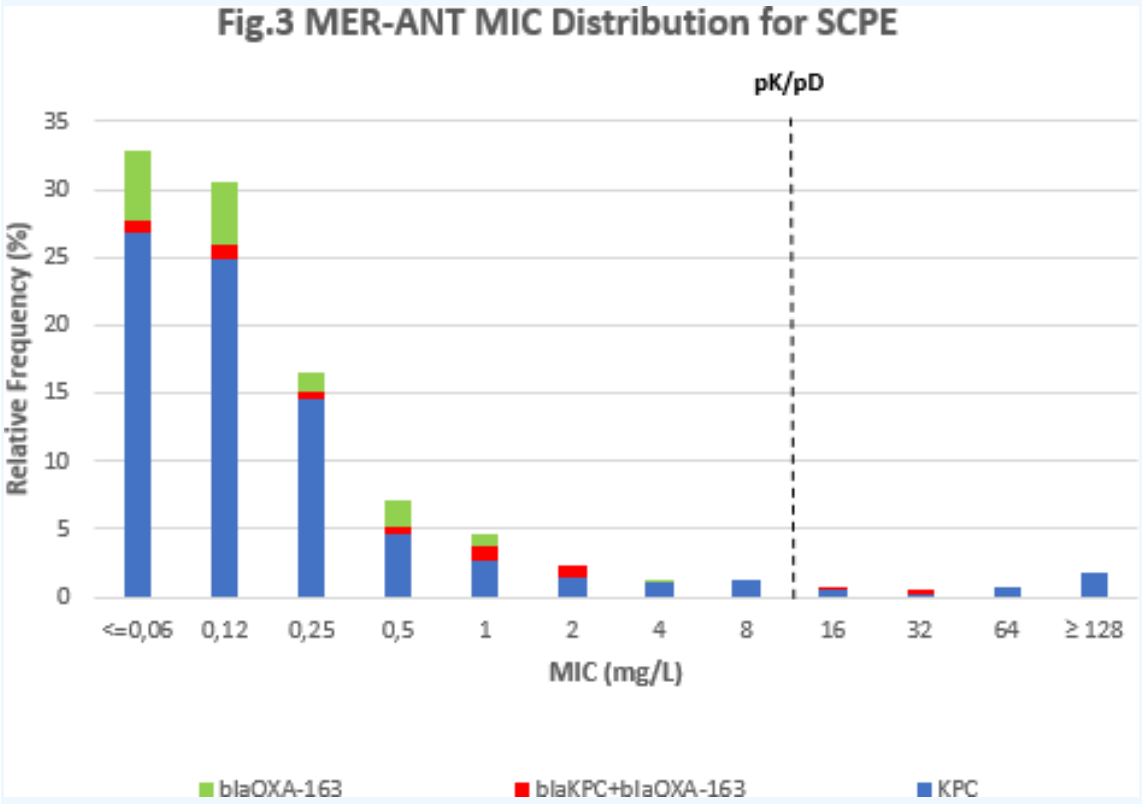
CBP	n	MER-ANT			IMR			CZA		
		MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range (mg/L)
KPC	327	0.12	1	<=0.06 - >=128	0.25	0,5	<=0.12-8	0,5	1	<=0.5 - >32
OXA	59	0.12	0.5	<=0.06 - 4	0.5	1	<=0.12-4	2	4	<=0.25 - 64
KPC + OXA	21	0.25	2	<=0.06 - 32	0.25	0,5	<=0.12-1	1	2	<=0.25 - 2
TOTAL	407	0.12	1	<=0.06 - >=128	0.25	1	<=0.12-8	<=0.5	2	<=0.25 - 64

CBP: Carbapenemase, MEM-ANT: Meropenem-ANT3310, IMR: Imipenem- relebactam, CZA: Ceftazidime-avibactam. Panel included (n): *K. pneumoniae* (325), *Enterobacter cloacae* (32), *Escherichia coli* (17), *Serratia marcescens* (12), *Morganellaceae*,(9) *Klebsiella aerogenes (7), Klebsiella oxytoca* (2), *Citrobacter freundii* (2) and *Citrobacter koseri* (1).

Fig.2 Antimicrobial Susceptibility Rates: Meropenem-ANT3310 and Comparator Agents.

CBP	n	% Susceptibility							
		MEM-ANT	IMR		CZA	COL	TIGE	AMK	FOS
		pK/pD	EUCAST	CLSI	CLSI-EUCAST				
KPC	327	96.0	98.5	98.2	97.2	68.8	66.3	66.8	71.1
OXA	59	98.3	95.1	91.8	95.1	78.0	68.3	51.7	71.7
KPC + OXA	21	90.5	100	100	100	31.6	83.3	65.0	65.0
TOTAL	407	96.3	98.3	97.5	97.8	68.4	67.4	64.5	70.9

CBP: Carbapenemase, MEM-ANT: Meropenem-ANT3310, IMR: Imipenem-relebactam, CZA: Ceftazidime-avibactam, COL: Colistin , TIGE: Tigecycline, AMK: Amikacin, FOS: Fosfomycin



Keyword 1
Antimicrobial susceptibility testing (AST)
Keyword 2
Antimicrobial resistance (AMR)
Keyword 3 (Please provide your suggestion)
KPC