Presentation
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Activity of BAL30072 and BAL30072 / Meropenem (1:1) Combination Against Recent Clinical Isolates of *Klebsiella pneumoniae* from Urinary Tract Infections.

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Abstract

Background: BAL30072 is an investigational intravenous monosulfactam antibiotic with bactericidal activity against a broad range of multidrug-resistant Gram-negative bacteria. It is currently in phase 1 clinical development. The objective of the present study was to investigate the activity of BAL30072 and the combination BAL30072 / meropenem (1:1) against 617 recent clinical isolates of *Klebsiella pneumoniae* from urinary tract infections.

Methods: A total of 617 isolates from 2012-2013 were tested and originated from Africa (n = 45), Asia (102), Europe (265), Latin America (133), Middle East (37), North America (20) and the Sout\h Pacific (15). Minimal inhibitory concentrations (MICs) were determined following CLSI microdilution guidelines.

Results: Results are shown in the Table 1 in the Results section of the poster.

Conclusions:. More than 50% of isolates were resistant to amoxicillin/clavulanic acid, aztreonam, gentamicin and levofloxacin, respectively, while resistance to meropenem was 16.2%. BAL30072 and meropenem exhibited MIC_{90} of >32 and 32 mg/L, respectively. However, BAL30072 / meropenem combination was more active with MIC_{90} of 4 mg/L. These data further suggest the potential utility of BAL30072 / meropenem combinations against drug-resistant UTI isolates of *K. pneumoniae*.

Introduction

BAL30072 is a novel sulfactam antibiotic with potent antimicrobial activity against a broad range of Gram-negative bacteria, including clinically increasingly problematic multidrug-resistant pathogens such as *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Klebsiella* spp. and *Enterobacter* spp.

BAL30072 is stable towards many types of beta-lactamases that can deactivate most of the currently marketed beta-lactam antibiotics such as cephalosporins and carbapenems [1-3]. The compound is taken up very readily into bacteria, exploiting essential nutrient uptake systems and is able to circumvent resistance caused by changes in the outer membrane of Gram-negative bacteria.

BAL30072 has been shown to be highly compatible with agents used for treating Gram-positive infections and preliminary data suggest BAL-30072 may act synergistically with some agents used for treating Gram-negative infections, such as carbapenems [1,4,5].

The objective of the present study was to investigate the activity of BAL30072 and the combination BAL30072 / meropenem (1:1) against recent clinical isolates of *Klebsiella pneumoniae* from urinary tract infections.

Methods

Clinical Isolates. A total of 617 recent clinical isolates of *K. pneumoniae* from urinary-tract infections were investigated. The isolates were collected in 2012 (n=439) and 2013 (n=178) from various geographical locations.

Susceptibility Testing. MIC tests were performed by broth microdilution (final volume 100 µl) against all isolates in line with CLSI susceptibility testing standards [6, 7]. Concurrent quality control testing using *Escherichia coli* ATCC 35218 and *E. coli* ATCC 25922 was performed as per CLSI guidelines [6]. BAL30072 was tested alone and as a meropenem/BAL30072 combination of 1:1 (MIC reported as the combined concentrations of both parts, eg. MIC of 1 mg/L = 0.5 mg/L meropenem + 0.5 mg/L BAL30072).

Geographic Distribution of Isolates. 617 *K. pneumoniae* isolates were collected from the following regions (n): Africa (45); Asia (102); Europe (265); Latin America (133); Middle East (37); North America (20) and South Pacific (15).

Results

Summary MIC data for BAL30072 alone and in combination with meropenem (1:1) against all 617 clinical isolates of *K. pneumoniae* are shown in Table 1. BAL30072 activity (as measured by MIC_{50}) was greater than most comparator agents (amoxicillin/clavulanic acid, aztreonam, gentamicin, levofloxacin & piperacillin-tazobactam) but less than meropenem alone, colistin or meropenem/BAL30072 in combination (Table 1).

Combination of BAL30072 with meropenem improved the activity of meropenem alone as demonstrated by lower MIC_{90} values against all *K. pneumoniae* combined (Table 2) and improved MIC distribution (Figure 1). This effect was also observed when data was analysed using isolates separated by geographical origin for all regions except Asia (Table 2).

Table 3 shows an analysis of the effect of BAL30072/meropenem combination on isolates stratified by meropenem MIC. It can be seen that the enhanced combination effect on mode or median MIC became apparent once meropenem MIC was greater than 0.25 µg/ml. This may explain the lack of combination effect on isolates from Asia because the meropenem MIC_{90} was low in this region (Table 2).

Table 1: Summary susceptibility data for BAL30072 and comparators against 617 clinical isolates of *K. pneumoniae*

Drug	Breakpoints (S|I|R)	% S	% I	% R	MIC_{50}	MIC_{90}	MIN	MAX
BAL30072	No Breakpoints Defined	-	-	-	1	> 32	<= 0.004	> 32
Meropenem	<=1 | 2 | >=4	80.2	3.6	16.2	0.06	32	<= 0.004	> 32
Meropenem/BAL30072 (1:1)*	No Breakpoints Defined	-	-	-	0.12	4	<= 0.008	> 64
Amoxicillin Clavulanic Acid	<=8/4 | 16/8 | >=32/16	15.2	26.1	58.7	32	> 32	<= 1	> 32
Aztreonam	<=4 | 8 | >=16	21.4	1.8	76.8	> 16	> 16	0.03	> 16
Colistin	No Breakpoints Defined	-	-	-	0.5	2	0.25	> 8
Gentamicin	<=4 | 8 | >=16	45.7	1.9	52.4	16	> 32	<= 0.12	> 32
Levofloxacin	<=2 | 4 | >=8	23.8	5.2	71.0	> 4	> 4	0.008	> 4
Piperacillin Tazobactam	<=16/4 | 32/4-64/4 | >=128/4	35.8	14.8	49.4	64	> 64	0.5	> 64

* Meropenem/BAL30072 (1:1) MIC reported as the combined concentration of meropenem and BAL30072

Table 2: Summary susceptibility data for BAL30072 with or without meropenem against clinical isolates of *K. pneumoniae* by geographical region.

Region (where N>30)		MIC (mg/L)		
		BAL30072	Meropenem	Meropenem/BAL30072 (1:1)*
ALL (617)	MIC_{50}	1	0.06	0.12
	MIC_{90}	> 32	32	4
Africa (45)	MIC_{50}	1	0.06	0.06
	MIC_{90}	32	16	0.5
Asia (102)	MIC_{50}	1	0.06	0.12
	MIC_{90}	> 32	0.25	0.5
Europe (265)	MIC_{50}	1	0.06	0.12
	MIC_{90}	> 32	> 32	8
Latin America (133)	MIC_{50}	1	0.06	0.12
	MIC_{90}	> 32	32	4
Middle East (37)	MIC_{50}	0.5	0.06	0.12
	MIC_{90}	32	> 32	1

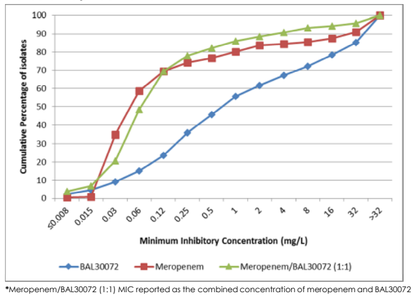
* Meropenem/BAL30072 (1:1) MIC reported as the combined concentration of meropenem and BAL30072

Table 3: Mode and geometric meropenem/BAL30072 MIC according to meropenem alone MIC

Meropenem MIC (mg/L)*	No isolates at MPM MIC	Meropenem/BAL30072 MIC (mg/L)**	
		Mode	Geometric mean
0.016	2	≤0.008	≤0.008
0.03	211	0.06	0.039
0.06	147	0.12	0.080
0.12	65	0.12	0.162
0.25	30	0.25	0.207
0.5	16	0.25	0.188
1	21	0.5	0.382
2	22	1	0.750
4	5	1	1.000
8	5	0.5	0.496
16	13	4	2.611
32	21	2	3.984

*Only data where full meropenem (MPM) MICs were determined.
** Meropenem/BAL30072 (1:1) MIC reported as the combined concentration of meropenem and BAL30072

Figure 1: Cumulative MIC distribution for meropenem and BAL30072 with or without meropenem against 617 clinical isolates of *K. pneumoniae*.



*Meropenem/BAL30072 (1:1) MIC reported as the combined concentration of meropenem and BAL30072

Conclusions

- BAL30072 activity (as measured by MIC_{50}) was greater than most comparator agents except meropenem alone or colistin.
- Combination of BAL30072 with meropenem improved the activity of meropenem alone against all *K. pneumoniae* combined and from separate regions of the world except Asia (where meropenem MIC_{90} was already low).
- Enhanced activity between meropenem and BAL30072 was most evident with those isolates possessing meropenem MIC of > 0.25 mg/L.
- These data support the data from previous studies where the presence of BAL30072 enhanced carbapenem activity [1,4,5].
- These data further suggest the potential utility of BAL30072 / meropenem combinations against drug-resistant UTI isolates of *K. pneumoniae*.

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