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Contemporary Arbekacin Activity When Tested against Clinical Bacteria Isolated from Patients Hospitalized with Pneumonia in United States (USA) Hospitals

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Abstract

Background: Arbekacin (ABK; ME1100) is a broad-spectrum aminoglycoside licensed for systemic use in Japan and under clinical development as inhalation solution in the USA. We evaluated the frequency of occurrence of organisms isolated from pneumonia in hospitalized patients (PHP), including ventilator-associated pneumonia (VAP), in the SENTRY Program (USA), and the activity of ABK tested against selected isolates.

Methods: Isolates were collected from 62 USA medical centers in 2012. Organism frequency was evaluated from a collection of 2,203 consecutively collected strains (339 from VAP); 904 were selected to be tested for susceptibility (S) by reference broth microdilution method against ABK and comparators.

Results: The 5 most common organisms from PHP (non-VAP/VAP) were (% of total): *S. aureus* ([SA] 34.1)/*P. aeruginosa* ([PSA] 29.2), PSA (20.0)/SA (28.3), *Klebsiella* spp. ([KSP] 8.7)/KSP (10.0), *Enterobacter* spp. ([ESP]) 6.2)/ESP (7.7) and *E. coli* (6.1)/*S. marcescens* (5.9). Against SA (43% MRSA), the highest ABK MIC was only 4 µg/ml (Table) and S rates (CLSI) for gentamicin (GEN), tobramycin (TOB) and amikacin (AMK) were 95.0, 76.0 and 96.0% respectively. For PSA, only 1 strain had ABK MIC >16 µg/ml and S rates for GEN, TOB and AMK were 88.0, 90.0 and 98.0%. PSA S to β-lactams was highest for ceftazidime (86.0%). ABK (MIC_{50}, 2 µg/ml) and TOB (MIC_{50}, 4 µg/ml) were the most active aminoglycosides tested against *A. baumannii*. Against Enterobacteriaceae, ABK and GEN ($MIC_{50/90}$, 0.25-1/1-8 µg/ml for both) were generally more active than TOB ($MIC_{50/90}$, 0.25-2/1-32 µg/ml) and AMK ($MIC_{50/90}$, 1-2/2-32 µg/ml). GEN was the most active aminoglycoside tested against *S. pneumoniae* and *H. influenzae*, followed by ABK and AMK.

Conclusions: SA and PSA were the most common causes of PHP (non-VAP and VAP) and isolated from >50% of the cases. ABK demonstrated potent activity and satisfactory coverage against the organisms most frequently isolated from PHP and VAP in USA hospitals. ABK activity was equal or superior to the most potent comparator in its class.

Organism (no. tested)	$MIC_{50/90}$ in µg/ml			
	Arbekacin	Gentamicin	Tobramycin	Amikacin
S. aureus (100)	0.25/0.5	0.25/0.5	0.5/>128	4/16
P. aeruginosa (100)	1/4	2/16	0.5/4	4/8
A. baumannii (100)	2/>128	64/>128	4/>128	8/>128
E. coli (102)	1/2	1/8	1/8	2/4
Enterobacter spp. (100)	0.5/1	0.5/1	0.5/1	1/2
K. pneumoniae (102)	0.25/8	0.25/8	0.25/32	1/32
S. marcescens (100)	1/2	0.5/1	2/4	2/4
S. pneumoniae (100)	32/64	16/16	-	64/128
H. influenzae (100)	4/4	2/2	-	8/16

Introduction

Arbekacin is a broad-spectrum aminoglycoside licensed for systemic use in Japan, where it is largely used to treat methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Arbekacin inhibits protein synthesis by binding both 50S and 30S ribosomal subunits and it is highly stable to most aminoglycoside modifying enzymes produced by *S. aureus*. Arbekacin spectrum of activity includes also Enterobacteriaceae species and non-fermentative Gram-negative bacilli, such as *Pseudomonas aeruginosa* and *Acinetobacter* spp.

Although arbekacin has demonstrated a broad spectrum of in vitro activity, it is licensed in Japan only for treatment of septicemia and pneumonia caused by MRSA. In the United States (USA), arbekacin is under clinical development as inhalation solution (development code: ME1100, https://clinicaltrials.gov/ct2/results?term=arbekacin&Search=Search) for the treatment of hospital-associated pneumonia, including ventilator-associated pneumonia (VAP). We evaluated the frequency of occurrence of organisms isolated from pneumonia in hospitalized patients (PHP), including VAP, in the SENTRY Antimicrobial Surveillance Program (USA, 2012), and the activity of arbekacin was determined against selected isolates.

Methods

Frequency of occurrence of bacterial organisms from patients hospitalized with pneumonia: Consecutive unique bacterial isolates were collected from 25 medical centers distributed across all nine USA Census Regions in 2012 as part of the SENTRY Program. Each participant center was requested to collect 100 consecutive bacterial isolates from lower respiratory tract sites determined to be significant by local criteria (Example: NNIS/ICARE/CDC) as the reported probable cause of pneumonia. The frequency of occurrence of organisms from patients with ventilator-associated pneumonia and those with pneumonia not ventilator-associated (all cases excluding VAP) were analyzed.

Evaluation of arbekacin activity - organism collection: The isolates were collected from 62 USA medical centers, in 2012, from patients hospitalized with bacterial pneumonia, including VAP. The most common specimen types were sputum (41.3%), tracheal aspirate (27.0%), bronchoalveolar lavage/wash (17.9%) and endotracheal tube (7.4%). Isolates were randomly selected from the SENTRY Program and had susceptibility patterns to key antimicrobial agents consistent with those observed in the SENTRY Program in the USA for 2012.

Evaluation of arbekacin activity - susceptibility methods: Reference broth microdilution tests were conducted according to the Clinical and Laboratory Standards Institute (CLSI M07-A9, 2012) methods. *S. aureus* and Gram-negative bacilli were tested in cation-adjusted Mueller-Hinton broth (CA-MHB), *S. pneumoniae* were tested in CA-MHB supplemented with 2.5-5% lysed horse blood, and *H. influenzae* strains were tested in Haemophilus Test Medium. CLSI interpretative criteria (M100-S24, 2014) were applied for the comparator agents. Concurrent testing of quality control (QC) strains per M07-A9 (2012) and M100-S24 (2014) documents assured proper test conditions. The QC strains tested (seven) were *S. aureus* ATCC 29213, *Escherichia coli* ATCC 25922 and 35218, *P. aeruginosa* ATCC 27853, *Streptococcus pneumoniae* ATCC 49619 and *Haemophilus influenzae* ATCC 49247 and 49766.

Results

- The five most common organisms from non-VAP were (% of total): *S. aureus* (34.1%), *P. aeruginosa* (20.0%), *Klebsiella* spp. (8.7%), *Enterobacter* spp. (6.2%) and *E. coli* (6.1%; Figure 1); whereas the five most common organisms from VAP were: *P. aeruginosa* (29.2%), *S. aureus* (28.3%), *Klebsiella* spp. (10.0%), *Enterobacter* spp. (7.7%) and *S. marcescens* (5.9%; Figure 2).
- When tested against *S. aureus* (43% MRSA), arbekacin activity (MIC_{50}, 0.25 µg/ml and MIC_{90}, 0.5 µg/ml; highest MIC, 4 µg/ml) was very similar to that of gentamicin (MIC_{50}, 0.25 µg/ml and MIC_{90}, 0.5 µg/ml) and greater than those of tobramycin (MIC_{50}, 0.5 µg/ml and MIC_{90}, >128 µg/ml) and amikacin (MIC_{50}, 4 µg/ml and MIC_{90}, 16 µg/ml). Susceptibility rates (CLSI) for gentamicin, tobramycin and amikacin were 95.0, 76.0 and 96.0% respectively (Table 1).
- Tobramycin (MIC_{50}, 0.5 µg/ml and MIC_{90}, 4 µg/ml; 90.0% susceptible) and arbekacin (MIC_{50}, 1 µg/ml and MIC_{90}, 4 µg/ml; 96.0% inhibited at ≤4 µg/ml) were the most potent (lowest MIC_{50} and MIC_{90} values) aminoglycoside tested against *P. aeruginosa*, followed by gentamicin (MIC_{50}, 2 µg/ml and MIC_{90}, 16 µg/ml; 88.0% susceptible) and amikacin (MIC_{50}, 4 µg/ml and MIC_{90}, 8 µg/ml; 98.0% susceptible; Table 1). *P. aeruginosa* susceptibility to β-lactams was highest for ceftazidime (86.0%) and piperacillin/tazobactam (78.0%; data not shown).
- Arbekacin (MIC_{50}, 2 µg/ml and MIC_{90}, >128 µg/ml; 65.0% inhibited at ≤4 µg/ml) and tobramycin (MIC_{50}, 4 µg/ml and MIC_{90}, >128 µg/ml; 51.0% susceptible) were also the most active aminoglycosides tested against *A. baumannii* (Table 1).
- Against Enterobacteriaceae, arbekacin and gentamicin (MIC_{50}, 0.25-1 µg/ml and MIC_{90}, 1-8 µg/ml for both compounds) were generally more active than tobramycin (MIC_{50}, 0.25-2 µg/ml and MIC_{90}, 1-32 µg/ml) and amikacin (MIC_{50}, 1-2 µg/ml and MIC_{90}, 2-32 µg/ml; Table 1).
- Gentamicin was the most active aminoglycoside tested against *S. pneumoniae* (MIC_{50} and MIC_{90}, 16 µg/ml) and *H. influenzae* (MIC_{50} and MIC_{90}, 2 µg/ml), followed by arbekacin (MIC_{50}, 32 µg/ml and MIC_{90}, 64 µg/ml for *S. pneumoniae* and MIC_{50} and MIC_{90} of 4 µg/ml for *H. influenzae*) and amikacin (MIC_{50}, 64 µg/ml and MIC_{90}, 128 µg/ml for *S. pneumoniae* and MIC_{50}, 8 µg/ml and MIC_{90}, 16 µg/ml for *H. influenzae*; Table 1).

Table 1. Frequency of occurrence of arbekacin and comparator aminoglycoside MIC values for the organisms tested.

Organisms (no. tested)	No. (cumulative %) of isolates inhibited at MIC (µg/ml)[a]:											
	≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
S. aureus (100)												
Arbekacin	1 (1.0)	54 (55.0)	38 (93.0)	6 (99.0)	0 (99.0)	1 (100.0)						
Gentamicin	4 (4.0)	64 (68.0)	25 (93.0)	1 (94.0)	1 (95.0)	0 (95.0)	0 (95.0)	0 (95.0)	1 (96.0)	2 (98.0)	1 (99.0)	1 (100.0)
Tobramycin	3 (3.0)	42 (45.0)	27 (72.0)	4 (76.0)	0 (76.0)	0 (76.0)	0 (76.0)	1 (77.0)	1 (78.0)	2 (80.0)	1 (81.0)	19(100.0)
Amikacin			2 (2.0)	6 (8.0)	40 (48.0)	25 (73.0)	12 (85.0)	11 (96.0)	3 (99.0)	0 (99.0)	0 (99.0)	1 (100.0)
S. pneumoniae (100)												
Arbekacin							2 (2.0)	12 (14.0)	38 (52.0)	46 (98.0)	2 (100.0)	
Gentamicin						3 (3.0)	35 (38.0)	60 (98.0)	2 (100.0)			
Amikacin								2 (2.0)	12 (14.0)	75 (89.0)	11 (100.0)	
P. aeruginosa (100)												
Arbekacin	2 (2.0)	3 (5.0)	16 (21.0)	31 (52.0)	26 (78.0)	18 (96.0)	1 (97.0)	2 (99.0)	0 (99.0)	1 (100.0)		
Gentamicin	2 (2.0)	3 (5.0)	10 (15.0)	34 (49.0)	30 (79.0)	9 (88.0)	1 (89.0)	2 (91.0)	4 (95.0)	2 (97.0)	0 (97.0)	3 (100.0)
Tobramycin	3 (3.0)	21 (24.0)	46 (70.0)	16 (86.0)	3 (89.0)	1 (90.0)	1 (91.0)	4 (95.0)	3 (98.0)	1 (99.0)	0 (99.0)	1 (100.0)
Amikacin		2 (2.0)	1 (3.0)	9 (12.0)	28 (40.0)	37 (77.0)	19 (96.0)	2 (98.0)	1 (99.0)	0 (99.0)	1 (100.0)	
A. baumannii (100)												
Arbekacin	2 (2.0)	6 (8.0)	21 (29.0)	15 (44.0)	14 (58.0)	7 (65.0)	6 (71.0)	5 (76.0)	2 (78.0)	4 (82.0)	1 (83.0)	17 (100.0)
Gentamicin	2 (2.0)	4 (6.0)	16 (22.0)	8 (30.0)	5 (35.0)	2 (37.0)	6 (43.0)	5 (48.0)	1 (49.0)	7 (56.0)	9 (65.0)	35 (100.0)
Tobramycin	1 (1.0)	5 (6.0)	21 (27.0)	14 (41.0)	6 (47.0)	4 (51.0)	6 (57.0)	5 (62.0)	1 (63.0)	7 (70.0)	7 (77.0)	23 (100.0)
Amikacin		1 (1.0)	1 (2.0)	16 (18.0)	19 (37.0)	11 (48.0)	7 (55.0)	3 (58.0)	6 (64.0)	12 (76.0)	6 (82.0)	18 (100.0)
E. coli (102)												
Arbekacin	1 (1.0)	1 (2.0)	28 (29.4)	59 (87.3)	8 (95.1)	2 (97.1)	2 (99.0)	1 (100.0)				
Gentamicin	1 (1.0)	3 (3.9)	46 (49.0)	34 (82.4)	6 (88.2)	0 (88.2)	2 (90.2)	0 (90.2)	1 (91.2)	5 (96.1)	4 (100.0)	
Tobramycin	1 (1.0)	2 (2.9)	36 (38.2)	42 (79.4)	5 (84.3)	2 (86.3)	4 (90.2)	5 (95.1)	2 (97.1)	3 (100.0)		
Amikacin				15 (14.7)	57 (70.6)	24 (94.1)	4 (98.0)	1 (99.0)	1 (100.0)			
Enterobacter spp.(100)												
Arbekacin		21 (21.0)	67 (88.0)	8 (96.0)	2 (98.0)	2 (100.0)						
Gentamicin	1 (1.0)	25 (26.0)	62 (88.0)	8 (96.0)	1 (97.0)	0 (97.0)	1 (98.0)	0 (98.0)	0 (98.0)	1 (99.0)	1 (100.0)	
Tobramycin	1 (1.0)	17 (18.0)	65 (83.0)	11 (94.0)	0 (94.0)	2 (96.0)	1 (97.0)	2 (99.0)	0 (99.0)	1 (100.0)		
Amikacin			1 (1.0)	55 (56.0)	37 (93.0)	5 (98.0)	2 (100.0)					
K. pneumoniae (102)												
Arbekacin	1 (1.0)	54 (53.9)	28 (81.4)	3 (84.3)	0 (84.3)	2 (86.3)	7 (93.1)	4 (97.1)	0 (97.1)	1 (98.0)	1 (99.0)	1 (100.0)
Gentamicin	2 (2.0)	51 (52.0)	28 (79.4)	3 (82.4)	2 (84.3)	5 (89.2)	2 (91.2)	0 (91.2)	1 (92.2)	2 (94.1)	2 (96.1)	4 (100.0)
Tobramycin	3 (2.9)	55 (56.9)	20 (76.5)	1 (77.5)	0 (77.5)	5 (82.4)	3 (85.3)	3 (88.2)	5 (93.1)	3 (96.8)	0 (96.8)	4 (100.0)
Amikacin			9 (8.8)	70 (77.5)	7 (84.3)	1 (85.3)	1 (86.3)	2 (88.2)	10 (98.0)	0 (98.0)	0 (98.0)	2 (100.0)
S. marcescens (100)												
Arbekacin			5 (5.0)	48 (53.0)	42 (95.0)	2 (97.0)	1 (98.0)	1 (99.0)	1 (100.0)			
Gentamicin		3 (3.0)	60 (63.0)	28 (91.0)	5 (96.0)	1 (97.0)	2 (99.0)	1 (100.0)				
Tobramycin			4 (4.0)	35 (39.0)	46 (85.0)	9 (94.0)	3 (97.0)	1 (98.0)	1 (99.0)	1 (100.0)		
Amikacin				15 (15.0)	70 (85.0)	12 (97.0)	2 (99.0)	1 (100.0)				
H. influenzae (100)												
Arbekacin				2 (2.0)	23 (25.0)	65 (90.0)	10 (100.0)					
Gentamicin			2 (2.0)	16 (18.0)	72 (90.0)	10 (100.0)						
Amikacin					4 (4.0)	32 (36.0)	53 (89.0)	11 (100.0)				

a. Underline indicates MIC_{50} and MIC_{90} values, and box indicates percentage susceptible by CLSI criteria (2014).

Figure 1. Frequency of occurrence of organisms from patients hospitalized with pneumonia (excluding ventilator-associated pneumonia [VAP]) in USA hospitals (n = 1,864; SENTRY Program, 2012).

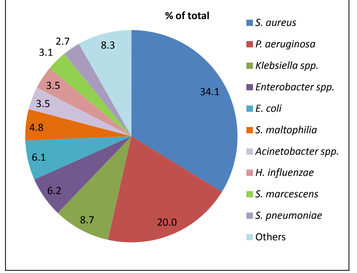
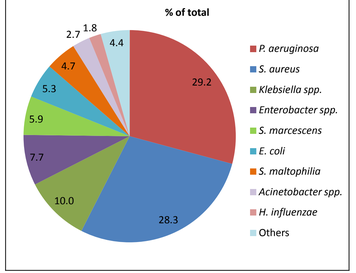


Figure 2. Frequency of occurrence of organisms from patients with ventilator-associated pneumonia (VAP) in USA hospitals (n = 339; SENTRY Program, 2012).



Conclusions

- *S. aureus* and *P. aeruginosa* were the most common causes of pneumonia in hospitalized patients (non-VAP and VAP) and isolated from >50% of the cases.
- Arbekacin demonstrated potent activity and satisfactory coverage against the organisms most frequently isolated from pneumonia in hospitalized patients, including VAP, in the USA hospitals evaluated.
- Arbekacin activity was similar or superior to the most potent comparator in its class (namely, amikacin, gentamicin and tobramycin).

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