

Arbekacin Tested against Well Characterized Multidrug-Resistant (MDR) Gram-negative Bacilli and Methicillin-Resistant *Staphylococcus aureus* (MRSA)

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Amended Abstract

Background: Arbekacin (ABK) is an aminoglycoside (AGC) with potent activity against *S. aureus* (SA), including methicillin-resistant strains (MRSA) and Gram-negative bacilli (GNB), including *P. aeruginosa* (PSA). We evaluated the activity of ABK tested against a global collection of MDR strains.

Methods: The organism collection (n=303) included: ESBL-producing *E. coli* (ESBL-EC; 33, including CTX-M [19], SHV [8], TEM [5] and OXA [1] producers), ESBL/KPC producing *K. pneumoniae* (ESBL/KPC-KPN; 78, including KPC-2/3 [40], CTX-M [16], SHV [22]), ceftazidime-resistant (CAZ-R; AmpC derepressed) *E. cloacae* (CAZ-R-ECL; 21) and *C. freundii* (CAZ-R-CF; 20), imipenem-resistant PSA (IMI-R-PSA; 31) and *A. baumannii* (IMI-R-ACB; 50), and MRSA (70; including hetero-VISA [20], community-acquired [CA-MRSA; 30] and gentamicin (GEN)-R [22] strains). Isolates were tested for susceptibility (S) by reference broth microdilution method against ABK and comparators.

Results: MIC₉₀ values of AGCs were generally elevated for ESBL-EC and ESBL/KPC-KPN (Table). Based on MIC₅₀, ABK was 2-, 4- and 16-fold more active than amikacin (AMK), GEN, and tobramycin (TOB) against ESBL-EC, respectively. ABK and GEN were the most active AGCs tested against ESBL/KPC-KPN, and ABK was active against 26.3 and 57.9% of GEN-non-S strains at ≤0.5 and ≤8 µg/ml, respectively. All AGCs exhibited good activity against CAZ-R-ECL, whereas ABK and AMK were the most active AGCs tested against CAZ-R-CF. ABK inhibited 64.5% of IMI-R-PSA at ≤8 µg/ml and was the most active AGC against this organism. None of the AGCs exhibited good activity against IMI-R-ACB. ABK was very active against MRSA (highest MIC, 4 µg/ml; 1 strain), including hVISA, CA-MRSA (MIC_{50/90}, 0.5/1 µg/ml for both groups) and GEN-R (MIC_{50/90}, 1/2 µg/ml) strains.

Conclusions: ABK consistently demonstrated the most potent in vitro activity against a wide collection of MDR GNB and MRSA strains and remained active against some of the strains R to other AGCs.

Organism (no. tested)	MIC _{50/90} in µg/ml (% S by CLSI):			
	Arbekacin	Amikacin	Gentamicin	Tobramycin
ESBL- <i>E. coli</i> (33)	2/32	4/32 (81.8)	8/>128 (48.5)	32/64 (27.3)
ESBL/KPC- <i>K. pneumoniae</i> (78)	8/16	16/64 (62.8)	4/256 (51.3)	32/64 (20.5)
CAZ-R <i>E. cloacae</i> (21)	0.5/1	2/2 (100.0)	0.5/1 (90.5)	1/1 (90.5)
CAZ-R <i>C. freundii</i> (20)	0.5/1	2/4 (95.0)	1/32 (80.0)	1/32 (75.0)
IMI-R <i>P. aeruginosa</i> (31)	4/64	8/512 (64.5)	16/>128 (38.7)	32/>128 (41.9)
IMI-R <i>A. baumannii</i> (50)	8/32	128/>512 (28.0)	128/>512 (14.0)	32/64 (24.0)
MRSA (70)	1/1	8/16 (90.0)	1/64 (68.6)	2/256 (51.4)

ESBL = extended-spectrum β-lactamase producing; CAZ-R = ceftazidime-resistant (MIC, ≥16 µg/ml); IMI-R = imipenem-resistant (MIC, ≥8 µg/ml).

Introduction

Arbekacin is a broad-spectrum aminoglycoside licensed for systemic use in Japan. Arbekacin spectrum of activity includes *Staphylococcus aureus*, Enterobacteriaceae species and non-fermentative Gram-negative bacilli, such as *Pseudomonas aeruginosa* and *Acinetobacter* spp. 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*.

Although arbekacin has demonstrated a broad spectrum of in vitro activity, it is only licensed in Japan for treatment of septicemia and pneumonia caused by MRSA. In the United States (USA), arbekacin is under clinical development for the treatment of HABP/VABP as inhalation solution (development code: ME1100, <https://clinicaltrials.gov/ct2/results?term=arbekacin&Search=Search>). We evaluated the activity of arbekacin tested against a global collection of well characterized multidrug-resistant strains.

Methods

Organism collection: The organism collection (n=303) comprised extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* (33, including CTX-M [19], SHV [8], TEM [5] and OXA [1] producing strains), ESBL/KPC producing *Klebsiella pneumoniae* (78, including KPC-2/3 [40], CTX-M [16], SHV [22]), ceftazidime-resistant (AmpC derepressed) *Enterobacter cloacae* (21) and *Citrobacter freundii* (20), imipenem-resistant *Pseudomonas aeruginosa* (31), imipenem-resistant *Acinetobacter baumannii* (50), and MRSA (70; including hetero-VISA [20], community-acquired [CA-MRSA; 30] and gentamicin-resistant [22] strains).

Susceptibility Methods: Reference broth microdilution tests were conducted according to the Clinical and Laboratory Standards Institute (CLSI; M07-A9, 2012) methods. Organisms were tested in cation-adjusted Mueller-Hinton broth and 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 (four) were *S. aureus* ATCC 29213, *E. coli* ATCC 25922 and 35218 and *P. aeruginosa* ATCC 27853.

Results

- MIC₉₀ values of aminoglycosides were generally elevated for ESBL-producing *E. coli* and ESBL/KPC-producing *K. pneumoniae* (Tables 1 and 2).

- Based on MIC₅₀, arbekacin (MIC₅₀, 2 µg/ml and MIC₉₀, 16 µg/ml) was 2-, 4- and 16-fold more active than amikacin (MIC₅₀, 4 µg/ml and MIC₉₀, 32 µg/ml), gentamicin (MIC₅₀, 8 µg/ml and MIC₉₀, >128 µg/ml), and tobramycin (MIC₅₀, 32 µg/ml and MIC₉₀, 512 µg/ml) against ESBL-producing *E. coli*, respectively (Tables 1 and 2).

- Arbekacin (MIC₅₀, 8 µg/ml and MIC₉₀, 16 µg/ml) and gentamicin (MIC₅₀, 4 µg/ml and MIC₉₀, 128 µg/ml) were the most active aminoglycosides tested against ESBL/KPC-producing *K. pneumoniae*, and arbekacin was active against 26.3 and 57.9% of gentamicin-non-susceptible strains at ≤0.5 and ≤8 µg/ml, respectively (Table 1). Only 14.1 and 47.4% of ESBL/KPC-producing strains were susceptible to ceftazidime and imipenem, respectively (Table 2).

- All aminoglycosides exhibited good activity against ceftazidime-resistant *E. cloacae* (MIC₅₀, 0.5-2 µg/ml and MIC₉₀, 1-2 µg/ml), whereas arbekacin (MIC₅₀, 0.5 µg/ml and MIC₉₀, 1 µg/ml) and amikacin (MIC₅₀, 2 µg/ml and MIC₉₀, 4 µg/ml) were the most active aminoglycosides tested against ceftazidime-resistant *C. freundii* (Tables 1 and 2).

- Arbekacin (MIC₅₀, 4 µg/ml and MIC₉₀, 64 µg/ml) inhibited 64.5% of imipenem-resistant *P. aeruginosa* at ≤8 µg/ml and was the most active aminoglycoside tested against this organism (Tables 1 and 2). Tobramycin (MIC₅₀, 32 µg/ml and MIC₉₀, >128 µg/ml) inhibited only 41.9% of strains at the CLSI susceptible breakpoint of ≤4 µg/ml (Table 2).

- None of the aminoglycosides exhibited good activity against imipenem-resistant *A. baumannii* (Table 2).

- Arbekacin was very active against MRSA (highest MIC, 4 µg/ml; one strain), including hVISA, CA-MRSA (MIC₅₀, 0.5 µg/ml and MIC₉₀, 1 µg/ml for both groups) and gentamicin-resistant strains (MIC₅₀, 1 µg/ml and MIC₉₀, 2 µg/ml; Table 1).

Table 1. Arbekacin MIC distributions when tested against multidrug-resistant organisms.

Organism (no. tested)	No. of isolates (cumulative %) inhibited at arbekacin MIC (µg/ml) of:									
	≤0.25	0.5	1	2	4	8	16	32	64	≥128
ESBL- <i>E. coli</i> (33)	2 (6.1)	5 (21.2)	8 (45.5)	4 (57.6)	4 (69.7)	3 (78.8)	2 (84.8)	3 (93.9)	1 (97.0)	1 (100.0)
ESBL/KPC- <i>K. pneumoniae</i> (78)	8 (10.3)	18 (33.3)	1 (34.6)	4 (39.7)	4 (44.9)	13 (61.5)	26 (94.9)	0 (94.9)	0 (94.9)	4 (100.0)
Gentamicin-non-susc. (38)	2 (5.3)	8 (26.3)	0 (26.3)	0 (26.3)	3 (34.2)	9 (57.9)	12 (89.5)	0 (89.5)	0 (89.5)	4 (100.0)
CAZ-R <i>E. cloacae</i> (21)	2 (9.5)	13 (71.4)	6 (100.0)	-	-	-	-	-	-	-
CAZ-R <i>C. freundii</i> (20)	-	14 (70.0)	4 (90.0)	0 (90.0)	0 (90.0)	1 (95.0)	1 (100.0)	-	-	-
IMI-R <i>P. aeruginosa</i> (31)	-	1 (3.2)	5 (19.4)	6 (38.7)	6 (58.1)	2 (64.5)	4 (77.4)	2 (83.9)	3 (93.5)	2 (100.0)
IMI-R <i>A. baumannii</i> (50)	-	1 (2.0)	5 (12.0)	6 (24.0)	8 (40.0)	9 (58.0)	10 (78.0)	8 (94.0)	1 (96.0)	2 (100.0)
MRSA (70)	5 (7.1)	27 (45.7)	34 (94.3)	3 (98.6)	1 (100.0)	-	-	-	-	-
Gentamicin-resistant (22)	-	7 (31.8)	11 (81.8)	3 (95.5)	1 (100.0)	-	-	-	-	-

Abbreviations: ESBL = extended-spectrum β-lactamase producing; KPC = *Klebsiella pneumoniae* carbapenemase; CAZ-R = ceftazidime-resistant (MIC, ≥16 µg/ml); IMI-R = imipenem-resistant (MIC, ≥8 µg/ml).

Table 2. Antimicrobial activity of arbekacin and comparator agents when tested against multidrug-resistant organisms.

Organisms ^a (no. tested)/ antimicrobial agent	MIC (µg/ml)			%S / %R ^b	Organisms ^a (no. tested)/ antimicrobial agent	MIC (µg/ml)			%S / %R ^b
	50%	90%	Range			50%	90%	Range	
ESBL-producing <i>E. coli</i> (33)					IMI-R <i>P. aeruginosa</i> (31)				
Arbekacin	2	16	0.25 – >512	- / -	Arbekacin	4	64	0.5 – >512	- / -
Amikacin	4	32	1 – >512	81.8 / 9.1	Amikacin	8	256	1 – >512	64.5 / 25.8
Gentamicin	8	>128	0.12 – >128	48.5 / 45.5	Gentamicin	16	>128	0.5 – >128	38.7 / 54.8
Tobramycin	32	512	0.25 – >512	27.3 / 60.6	Tobramycin	32	>128	0.25 – 512	41.9 / 54.8
Ceftazidime	16	512	0.25 – >512	42.4 / 57.6	Ceftazidime	64	>512	2 – 128	32.3 / 61.3
Imipenem	0.25	0.5	0.12 – 0.5	100.0 / 0.0	Imipenem	16	256	8 – >512	0.0 / 100.0
ESBL/KPC-producing <i>K. pneumoniae</i> (78)					IMI-R <i>A. baumannii</i> (50)				
Arbekacin	8	16	0.25 – >512	- / -	Arbekacin	8	32	0.5 – >512	- / -
Amikacin	16	64	0.5 – >512	62.8 / 17.9	Amikacin	128	>512	1 – >512	28.0 / 62.0
Gentamicin	4	>128	0.25 – >128	51.3 / 35.9	Gentamicin	128	>128	0.25 – >128	14.0 / 84.0
Tobramycin	32	64	0.25 – >512	20.5 / 67.9	Tobramycin	32	64	0.5 – >512	24.0 / 64.0
Ceftazidime	128	512	1 – >512	14.1 / 79.5	Ceftazidime	128	>512	0.25 – >512	10.0 / 88.0
Imipenem	2	64	≤0.06 – 256	47.4 / 50.0	Imipenem	64	128	8 – 256	0.0 / 100.0
CAZ-R <i>E. cloacae</i> (21)					MRSA (70)				
Arbekacin	0.5	1	0.25 – 1	- / -	Arbekacin	1	1	0.12 – 4	- / -
Amikacin	2	2	0.5 – 4	100.0 / 0.0	Amikacin	8	16	1 – 256	90.0 / 2.9
Gentamicin	0.5	1	0.25 – 128	90.5 / 9.5	Gentamicin	1	64	0.12 – >128	68.6 / 31.4
Tobramycin	1	1	0.25 – 32	90.5 / 4.8	Tobramycin	2	256	0.5 – >512	51.4 / 48.6
Ceftazidime	64	128	32 – 256	0.0 / 100.0					
Imipenem	0.5	1	0.12 – 1	100.0 / 0.0					
CAZ-R <i>C. freundii</i> (20)									
Arbekacin	0.5	1	0.5 – 16	- / -					
Amikacin	2	4	1 – 64	95.0 / 5.0					
Gentamicin	1	32	0.5 – >128	80.0 / 20.0					
Tobramycin	1	32	0.5 – 256	75.0 / 25.0					
Ceftazidime	128	128	16 – 256	0.0 / 100.0					
Imipenem	0.5	1	0.25 – 1	100.0 / 0.0					

a. Abbreviations: ESBL = extended spectrum β-lactamase, CAZ-R = ceftazidime-resistant (MIC, ≥16 µg/ml); IMI-R = imipenem-resistant (MIC, ≥8 µg/ml), MRSA = methicillin-resistant *S. aureus*.
b. Criteria as published by the CLSI (2014).

Conclusions

- Arbekacin demonstrated potent in vitro activity against a wide collection of multidrug-resistant Gram-negative bacilli and remained active against some of the strains resistant to other aminoglycosides
- Arbekacin was highly active against MRSA strains, including those resistant to gentamicin.

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