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REVIEW

Arbekacin: another novel agent for treating infections due to methicillin-resistant *Staphylococcus aureus* and multidrug-resistant Gram-negative pathogens

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Abstract: Arbekacin sulfate (ABK), an aminoglycoside antibiotic, was discovered in 1972 and was derived from dibekacin to stabilize many common aminoglycoside modifying enzymes. ABK shows broad antimicrobial activities against not only Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) but also Gram-negative bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. ABK has been approved as an injectable formulation in Japan since 1990, under the trade name Habekacin, for the treatment of patients with pneumonia and sepsis caused by MRSA. The drug has been used in more than 250,000 patients, and its clinical benefit and safety have been proven over two decades. ABK currently shows promise for the application for the treatment of multidrug-resistant Gram-negative bacterial infections such as multidrug-resistant strains of *P. aeruginosa* and *Acinetobacter baumannii* because of its synergistic effect in combination with beta-lactams.

Keywords: synergistic effect, Habekacin, MRSA, multidrug-resistant Gram-negative bacteria

Introduction

Arbekacin (ABK) (Meiji Seika Pharma Co, Ltd, Tokyo, Japan) has the hydroxy aminobutyryl group as its chemical structure and is classified as a kanamycin family aminoglycoside (Figure 1).[1] ABK causes membrane damage and binds both to the 50S and the 30S ribosomal subunits, resulting in codon misreading and inhibition of translation.[2] ABK is not inactivated by aminoglycoside-inactivating enzymes such as (3′) aminoglycoside-phosphotransferase (APH), (4′) aminoglycoside-adenyltransferase (AAD), or AAD (2″) and has a weak affinity for (6′-IV) aminoglycoside-acetyltransferase (AAC). Therefore, ABK exhibits antimicrobial activity against Gram-positive and -negative pathogens including strains resistant to gentamicin (GM), tobramycin (TOB), and amikacin (AMK). In particular, ABK has strong antimicrobial potency against methicillin-resistant *Staphylococcus aureus* (MRSA) and has been used in Japan since 1990 under the trade name Habekacin (Meiji Seika Pharma Co., Ltd. Tokyo, Japan), to treat sepsis and pneumonia caused by MRSA. In addition, Habekacin has also been used in Korea since 2000.

Principal pharmacology (in vitro antibacterial activities)

ABK showed strong antimicrobial activity against Gram-positive bacteria such as *S. aureus*[3] and *Staphylococcus epidermidis*.[4] Antibacterial activities of ABK, GM, TOB, and AMK against 54 methicillin-susceptible *S. aureus* clinical isolates were determined

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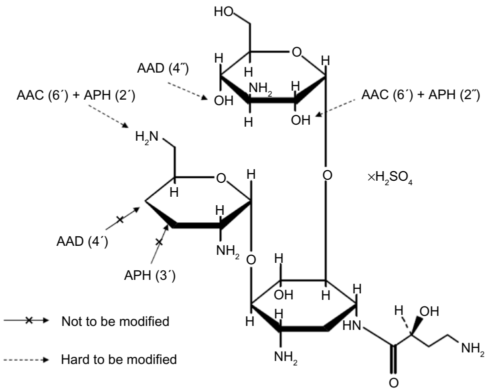

Figure 1 Structural formula of arbekacin sulfate.
Abbreviations: APH, aminoglycoside-phosphotransferase; AAD, aminoglycoside-adenyltransferase; AAC, aminoglycoside-acetyltransferase.

and the results are shown in Table 1.[3] The minimal inhibitory concentration (MIC) for 90% of the organisms (MIC_{90}) of ABK was 1 μg/mL, whereas MIC_{90} of GM, TOB, and AMK were 4, 8, and 16 μg/mL, respectively.[3] Furthermore, the MIC_{90} of ABK against *S. epidermidis* was 0.5 μg/mL and it was stronger than that of AMK (MIC_{90} 4 μg/mL).[4] ABK also has superior antibacterial activity against Gram-negative bacteria including *Pseudomonas aeruginosa*.[3,5]

The antibacterial activities of ABK against strains producing aminoglycoside-inactivating enzymes were investigated as well as the antibacterial activities of ABK against tested organisms without the influence of aminoglycoside-inactivating enzymes.[6] The bactericidal effects of ABK against *S. aureus* and *Escherichia coli* were better than those of AMK and GM, and the bactericidal effects against *Klebsiella pneumoniae* and *P. aeruginosa* were comparable with AMK and GM.[7]

Stability to aminoglycoside-inactivating enzymes

ABK was stable to the aminoglycoside-inactivating enzymes produced by MRSA, such as APH, AAD, and AAC.[8] Although GM, AMK, TOB, and kanamycin (KM) were completely inactivated by APH (2″), ABK still showed about 50% activity against APH (2″). Furthermore, ABK was not inactivated by AAD (4′) and APH (3′), and also showed stability to these enzymes. These results suggest the excellent antibacterial activities of ABK against MRSA strains.

Antibacterial activity against MRSA

ABK showed the most potent antibacterial effect against clinically isolated MRSA strains among the tested aminoglycosides (GM, TOB, and AMK), and the antibacterial effect of ABK was equivalent to that of vancomycin (VCM).[3,9–12] Figure 2 shows the cumulative percentage of MIC against MRSA with

Table 1 In vitro antibacterial activity against aerobic bacteria

Bacterial strain	(μg/mL)	Antibacterial agent						
		Gentamicin	Tobramycin	Amikacin	Arbekacin	Vancomycin	Teicoplanin	Linezolid
Methicillin-resistant *Staphylococcus aureus* (n=76)	MIC_{50}	16	≥256	16	0.5	1	0.5	2
	MIC_{90}	128	≥256	32	1	2	2	2
	Range	0.125 to ≥256	0.25 to ≥256	1 to ≥256	0.125 to 4	0.5 to 2	0.125 to 4	1 to 4
Methicillin-susceptible *S. aureus* (n=54)	MIC_{50}	0.25	0.5	2	0.5	1	0.5	2
	MIC_{90}	16	8	4	1	2	1	2
	Range	0.125 to 64	0.125 to 32	0.5 to 8	0.125 to 1	0.5 to 2	0.25 to 2	1 to 4
Streptococcus pneumoniae (n=127)	MIC_{50}	4	16	32	16	0.25	≤0.06	1
	MIC_{90}	8	16	64	32	0.5	0.125	1
	Range	2 to 16	4 to 32	16 to 128	8 to 64	0.125 to 0.5	≤0.06 to 0.125	0.125 to 2
Haemophilus influenzae (n=123)	MIC_{50}	1	2	4	2	nt	nt	nt
	MIC_{90}	1	2	8	4	nt	nt	nt
	Range	0.125 to 4	0.5 to 8	0.5 to 8	0.5 to 8	nt	nt	nt
Moraxella catarrhalis (n=70)	MIC_{50}	0.125	0.25	0.5	0.125	64	16	8
	MIC_{90}	0.125	0.25	1	0.25	128	32	8
	Range	≤0.06 to 0.25	≤0.06 to 0.5	≤0.06 to 2	≤0.06 to 0.5	32 to 128	8 to 32	2 to 16
Klebsiella pneumoniae (n=78)	MIC_{50}	0.25	0.5	1	0.5	nt	nt	nt
	MIC_{90}	0.25	0.5	1	0.5	nt	nt	nt
	Range	≤0.06 to 0.5	≤0.06 to 8	0.125 to 2	≤0.06 to 0.5	nt	nt	nt
Pseudomonas aeruginosa (n=103)	MIC_{50}	1	0.5	2	1	nt	nt	nt
	MIC_{90}	8	2	8	8	nt	nt	nt
	Range	≤0.06 to ≥256	≤0.06 to ≥256	0.125 to 64	0.125 to 32	nt	nt	nt

Note: Inoculum size: 10^6 CFU/mL.
Abbreviations: nt, not tested; CFU, colony forming units; MIC, minimal inhibitory concentration; MIC_{90}, minimal inhibitory concentration for 90% of the organisms; MIC_{50}, minimal inhibitory concentration for 50% of the organisms.

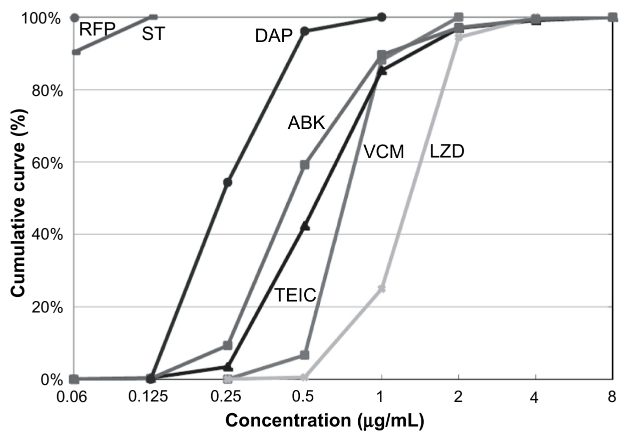

Figure 2 Antibacterial activity against MRSA.
Notes: The surveillance was jointly conducted by the Surveillance Committee of Japanese Society of Chemotherapy, Japanese Association for Infectious Diseases, and Japanese Society for Clinical Microbiology. VCM, TEIC, ABK, and LZD: n=557; ST, RFP, and DAP: n=103.
Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; VCM, vancomycin; TEIC, teicoplanin; ABK, arbekacin; LZD, linezolid; ST, sulfamethoxazole-trimethoprim; RFP, rifampicin; DAP, daptomycin.

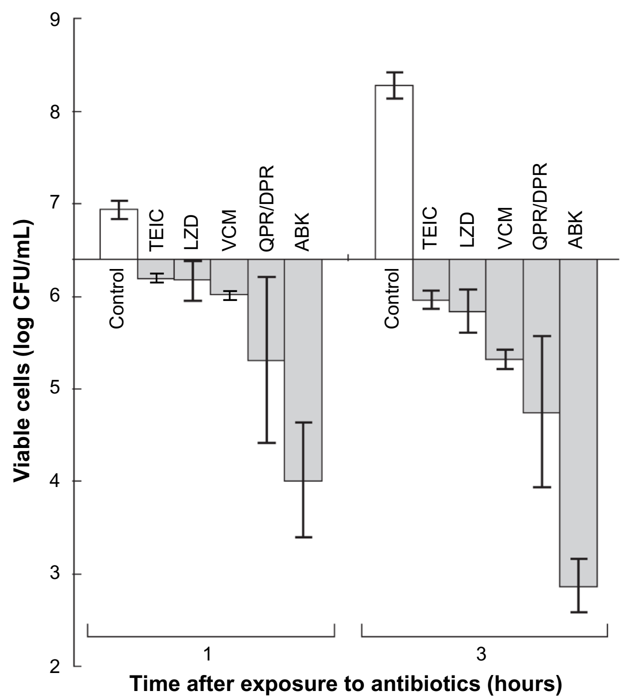

Figure 3 Bactericidal activity of anti-MRSA agents against five MRSA strains.
Notes: Boxes and bars indicate mean and SD of viable cell counts. Mean ± SD of viable cell count (log of CFU/mL) before exposure to antibiotics was 6.40±0.06.
Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; TEIC, teicoplanin; LZD, linezolid; VCM, vancomycin; QPR/DPR, quinupristin/dalfopristin; ABK, arbekacin; SD, standard deviation; CFU, colony forming units.

the antimicrobial susceptibility surveillance conducted in Japan.[9–12] The antimicrobial activity of ABK was more potent than the other anti-MRSA drugs except daptomycin.

The susceptibility of MRSA to ABK has not changed since 1990 when ABK was launched. In another surveillance, the MICs of ABK, VCM, teicoplanin (TEIC), and linezolid (LZD) against 228 MRSA clinical isolates in Japan were determined. The results showed that MIC_{90}/MIC_{50} of VCM and ABK had not significantly changed in the period from 1990 to 2006 even though MIC_{90} of TEIC and LZD were slightly increased during the period.[13]

Bactericidal effect of ABK against MRSA

ABK also shows concentration-dependent bactericidal activity.[14–18] Viable counts of MRSA were rapidly decreased in a short period after the addition of ABK in comparison with those of VCM, TEIC, and LZD (Figure 3).[18]

Post antibiotic effect of ABK

Post antibiotic effect is another characteristic of aminoglycoside antibiotics. When MRSA was treated either with ABK or VCM with the same concentration, the bactericidal activity of VCM was weaker than ABK, and the post antibiotic effect was shorter compared with ABK.[14]

Inhibition of toxic shock syndrome toxin-1 (TSST-1) by ABK

The effect of ABK, VCM, and TEIC on the production of TSST-1 by MRSA strains has been reported.[19] In logarithmic phase cultures, ABK, VCM, and TEIC inhibited TSST-1 production by 85, 10, and 25%, respectively, at the concentration of one fourth of each MIC (Figure 4).

Antibacterial activities against multidrug-resistant *P. aeruginosa*

Multidrug-resistant strains of *P. aeruginosa* have been an important issue and the strains with the MICs of AMK ≥32 µg/mL, imipenem ≥16 µg/mL, and ciprofloxacin ≥4 µg/mL are defined as multidrug-resistant *P. aeruginosa* (MDRP) in Japan. It is difficult to treat patients with MDRP infections and colistin (CL) may be a good candidate for treatment. Because CL is not approved for clinical use in Japan, many doctors in Japan are interested in combination therapy such as beta-lactam antibiotics and aminoglycoside antibiotics.

Antibiotic combination therapy study groups studied the effective combination regimen against MDRP and demonstrated that ABK plus aztreonam (AZT) was the most promising combination, the other promising regimens were AZT plus AMK and AZT plus GM (Figure 5).[20]

Antibiotic combination therapy study groups also reported that a combination of ABK plus AZT showed

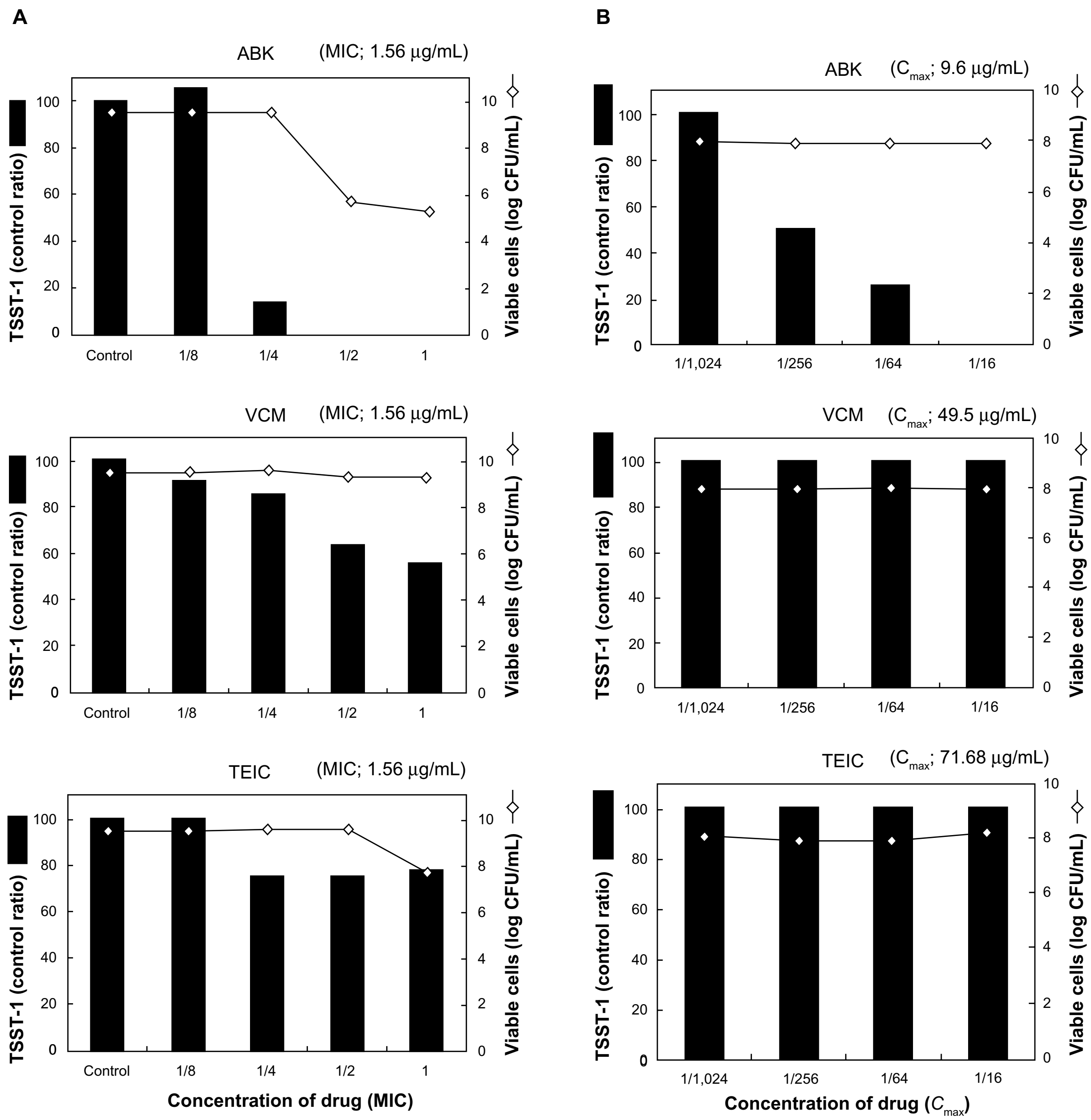

Figure 4 Effect of TSST-1 producing ability of MRSA.

Notes: (**A**) Effect on TSST-1 production in logarithmic growth phase; (**B**) effect on TSST-1 production of blood-containing medium. 1 MIC values of test drugs against *S. aureus* Sak-1 were all 1.56 μg/mL. The 1/2, 1/4, and 1/8 MIC values were 0.78, 0.39, and 0.195 μg/mL, respectively. C_{max} is the maximum concentration of serum after the administration of each drug in humans using the usual dose, and these values were 9.6 μg/mL for ABK, 49.5 μg/mL for VCM and 71.68 μg/mL for TEIC, respectively. Then, 1/16, 1/64, 1/256 and 1/1024 C_{max} were calculated using the C_{max} of each drug.

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; ABK, arbekacin; VCM, vancomycin; TEIC, teicoplanin; TSST-1, toxic shock syndrome toxin-1; CFU, colony forming units; MIC, minimal inhibitory concentration; C_{max}, maximum concentration.

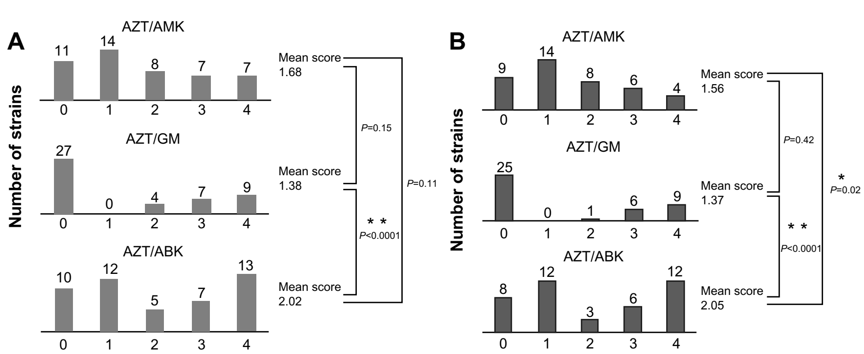

Figure 5 Scoring of combination effect for each drug combination against multidrug-resistant (MDR) *Pseudomonas aeruginosa* strains.

Notes: (**A**) All 47 MDRPs. (**B**) N=41 metallo-beta-lactamase (MBL)-positive MDRP strains.

Abbreviations: MDRP, multidrug-resistant *Pseudomonas aeruginosa*; AZT, aztreonam; AMK, amikacin; GM, gentamicin; ABK, arbekacin.

synergistic effects as well as the combinations of CL plus rifampin, and AMK plus AZT (Figure 6).[21] These results suggest that ABK is a useful agent for MDRP infections used in combination therapies.

Antibacterial activities against multidrug-resistant *Acinetobacter baumannii-calcoaceticus*

Recently, ABK has also attracted attention for its antibacterial effect against *A. baumannii-calcoaceticus.* Zapor et al[22] examined the in vitro antibacterial activity of ABK against *A. baumannii-calcoaceticus* isolated from clinical specimens at The Walter Reed Army Medical Center during the Global War on Terrorism. Additionally, the in vitro MIC of ABK against 200 *Acinetobacter baumannii-calcoacetics* isolates recovered from wounded soldiers was determined. The median MIC was 2 μg/mL (range: 0.5 to >64 μg/mL). A total of 97.5% of the isolates had ABK MICs of <8 μg/mL and 86.5% had MICs of <4 μg/mL. There was no association between the ABK MIC and susceptibility to 16 other antibiotics or the specimen source. Moreover, synergy testing suggested an enhanced effect of ABK-carbapenem combinations.[22]

Efficacy in mouse mixed infection model (in vivo)

Since ABK has shown potent activities against both MRSA and *P. aeruginosa*, the effect of ABK in a mixed infection model using MRSA and *P. aeruginosa* was investigated. The median effect dose (ED_{50}) that calculated the life and death on 7 days after administration was 19.5 mg/kg for ABK and >100 mg/kg for VCM. Thus, ABK showed a protective polymicrobial effect on MRSA and *P. aeruginosa* infections.[23]

Pharmacokinetics in adults

A multi-center collaborative open clinical study was conducted in patients infected with MRSA to evaluate the efficacy, safety, and the pharmacokinetics-pharmacodynamics (PK-PD) of ABK. The patients were administered 200 mg of ABK once daily, and the patients with severe renal dysfunction (creatinine clearance ≥80 mL/min) showed changes in the pharmacokinetic parameters such as prolongation of half-life, decrease of total clearance, and increase of area under the curve (0–24 hr) (AUC_{0-24}) (Table 2 and Figure 7A).[24]

On the other hand, the pharmacokinetics in healthy volunteers with normal renal function did not change on 400 and 600 mg single dose or on multiple administrations of ABK over a period of 7 days (Table 2 and Figure 7B).[25] These data suggest that renal clearance and total clearance do not decrease at a high dose, and ABK has no tendency toward accumulation if renal function is normal.

Pharmacokinetics in children

Recommended initial dosing regimens were 5 mg/kg every 48 hours for preterm infants (postnatal age was within 28 days), 5 mg/kg every 24 hours for preterm infants (postnatal age was 28 days or more), and 4 mg/kg every 24 hours for term infants. These initial dosing regimens could manage the maximum concentration (C_{max}) 7–15 μg/mL and trough concentration (C_{trough}) 0–2 μg/mL in 72.2%–93.5% of infant patients.[26]

Administration of ABK once daily in neonates has been investigated; the mean serum peak and C_{trough} of ABK were 15.2±4.3 μg/mL and 2.0±1.4 μg/mL, respectively. Overall clinical effectiveness was 78.9% and no adverse effect was observed. During the period of administration, serum creatinine levels of some cases increased slightly, although the highest was 0.27 mg/dL but returned to baseline (pre-dose value) promptly after stopping ABK administration. Therefore, it is supposed that ABK therapy once daily in neonates is a treatment option.[27]

Distribution of ABK

The PK-PD parameters of ABK in bronchial epithelial lining fluid (ELF) were investigated and the mean C_{max} in serum and bronchial ELF were 26.0±12.2, and 10.4±1.9 μg/mL, respectively.[28] The ratio of concentrations of the drug in bronchial

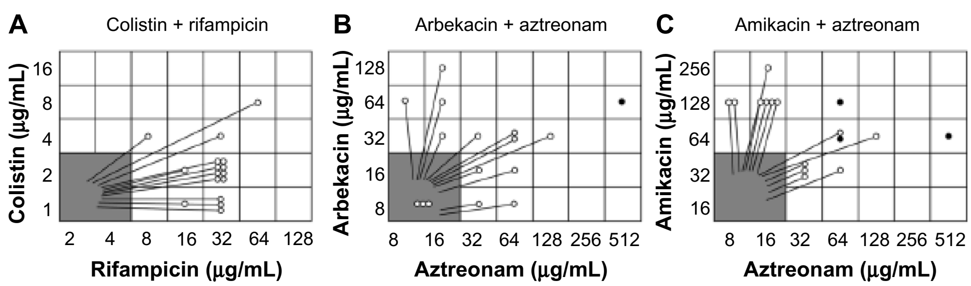

Figure 6 Results of Break-point Checkerboard Plate for (**A**) colistin plus rifampicin, (**B**) arbekacin plus aztreonam and (**C**) amikacin plus aztreonam.
Notes: The gray area indicates the drug concentration using the Break-point Checkerboard Plate. The open circles indicate the strains judged as "effective" and the closed circles indicate the strains judged as "non-effective".

Table 2 Pharmacokinetic parameters after administration of ABK

Group		C_{max} (μg/mL)	C_{trough} (μg/mL)	$T_{1/2}$ (hr)	$AUC_{0–24}$ (μg·hr/mL)	CL_{tot} (L/hr)	V_{ss} (L)	Reference
All patients	n	17	17	12	12	12	12	24
	Mean ± SD	16.2±5.1	1.1±1.7	8.06±7.44	103.1±66.4	2.61±1.69	15.3±3.6	
	Min–max	7.2–23.1	0.0–5.3	1.96–23.73	36.5–222.4	0.56–5.47	10.4–20.2	
Normal renal function	n	10	10	5	5	5	5	
80≦ Ccr	Mean ± SD	15.2±5.7	0.3±0.4	3.51±2.67	58.6±22.5	3.71±1.31	14.6±4.3	
	Min–max	7.2–23.1	0.0–1.2	1.96–8.3	36.5–96.3	1.81–5.47	10.4–20.2	
Mild renal dysfunction	n	3	3	3	3	3	3	
50≦ Ccr <80	Mean ± SD	14.8±2.4	0.2±0.3	3.95±2.32	62.9±18.0	3.30±1.06	15.9±3.9	
	Min–max	12.4–17.3	0.0–0.6	2.51–6.63	45.6–81.5	2.27–4.38	11.6–19.3	
Moderate to severe	n	4	4	4	4	4	4	
renal dysfunction	Mean ± SD	19.8±3.7	3.9±1.1	16.82±6.02	188.8±24.0	0.7±0.14	15.7±3.5	
Ccr <50	Min–max	14.6–23.1	2.7–5.3	10.27–23.73	165.3–222.4	0.56–0.87	10.6–18.5	
Dose	**n=8**	**C_{max} (μg/mL)**	**C_{peak} (μg/mL)**	**$T_{1/2}$ (hr)**	**$AUC_{0\text{-infinity}}$ (μg·hr/mL)**	**CL_{tot} (L/hr)**	**V_{ss} (L)**	**Reference**
400 mg Day 7	Mean ± SD	44.4±5.3	25.6±2.1	6.4±1.7	107.5±17.1	3.8±0.6	18.6±3.4	25
600 mg Day 7	Mean ± SD	68.9±5.4	38.0±2.8	4.1±1.6	149.9±12.9	4.0±0.3	14.5±2.8	

Abbreviations: ABK, arbekacin; Ccr, creatinine clearance (mL/min); SD, standard deviation; C_{max}, maximum concentration; C_{trough}, trough concentration; $T_{1/2}$, half-life; AUC, area under the curve; CL_{tot}, total clearance; min, minimum; max, maximum; Vss, distribution volume at steady state.

ELF to C_{max} in serum was 0.465±0.188. These data suggest that transitivity of ABK to the respiratory tract was relatively good, because transitivity of aminoglycosides to the lungs is about 30% in general.[29]

It has been reported that volume of distribution of aminoglycosides generally correlates with the extracellular fluid[30,31] and tissue fluids, such as interstitial fluid or synovial fluid, with a sufficient concentration of the drug infiltrating a surgical wound site and subcutaneous tissue.[32–38] Distribution of ABK from circulating blood to a wound site was evaluated in patients with wound infection caused by *S. aureus* who were treated with 200 mg of ABK once daily. In this study, high levels of distribution in the wound exudate, 46.2%–55.3%, were observed.[39]

Therapeutic drug monitoring of ABK

Therapeutic drug monitoring (TDM) of ABK is required for maximizing efficacy while minimizing toxicities. In the population of patients with normal renal function, the target

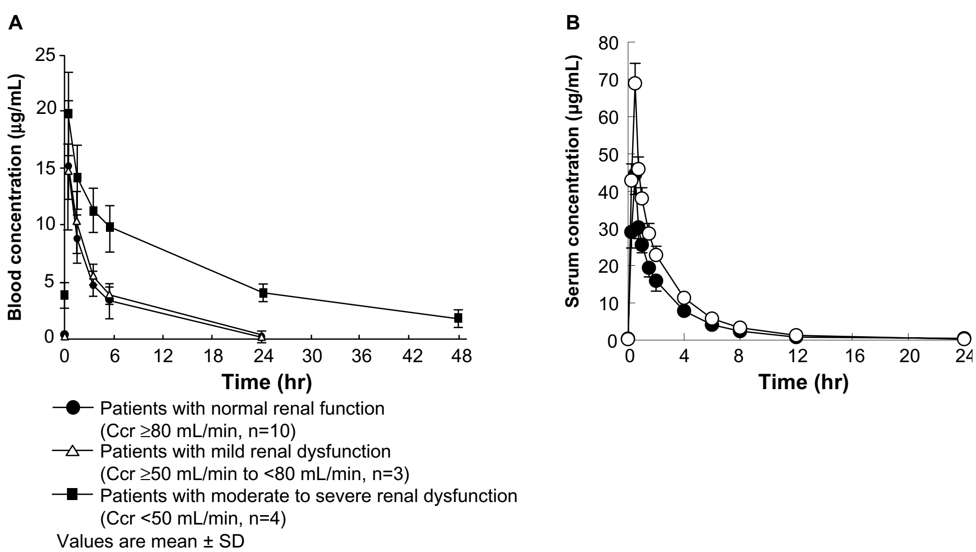

Figure 7 Plasma (serum) concentration after administration of ABK.

Notes: (**A**) Plasma concentration after administration of ABK 200 mg for MRSA infected adult patients; (**B**) serum concentrations of ABK in healthy adults after multiple administrations of ABK 400 mg (closed circles) or 600 mg (open circles). Mean ± SD (n=8).

Abbreviations: ABK, arbekacin; MRSA, methicillin-resistant *Staphylococcus aureus*; SD, standard deviation; Ccr, creatinine clearance (mL/min).

peak concentration (C_{peak}) value of 15–20 μg/mL was not achieved with once daily administration of 150–200 mg as the approved dose, and a higher dosing regimen is required to improve clinical efficacy. A clinical practice guideline for TDM of ABK was developed by the Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring.[40] Experts recommend 300 mg/day (5.5–6.0 mg/kg) to reach the target concentration.

PK-PD parameters

The PK-PD parameter of ABK which was associated with a therapeutic effect was C_{max}/MIC and/or AUC/MIC, with a low correlation of efficacy observed in T>MIC, and the highest correlation coefficient observed in C_{max}/MIC.[41–43] It was shown that the probability of cure/improvement rose when the C_{max} of ABK was increased, with an odds ratio of 6.7 for a change in C_{max} from 7.9–12.5 μg/mL.[44] In other studies, a key determinant of clinical efficacy of ABK was considered to be C_{max}/MIC, and the appropriate C_{max}/MIC value which showed a good correlation between bacteriological efficacy was 8 or higher.[44–48]

Clinical efficacy

There are several reports on clinical efficacy, bacteriological efficacy, and safety against MRSA infection which compared the treatment of VCM and ABK.[49,50] Hwang et al[50] reported that the bacteriological efficacy responses of ABK and VCM were 71.2% and 79.5%, respectively, and the clinical efficacy responses of those were 65.3% and 76.1%, respectively, and that there was no statistically significant difference between ABK and VCM. The incidence of complications was significantly higher in the VCM group (32.9%) in comparison with the ABK group (15.1%) (P=0.019). ABK was not inferior to VCM, and it could be a good alternative drug for the treatment of MRSA infection.[49] However, further prospective randomized trials are needed to confirm this finding.[50]

Clinical trial for re-assessment of higher dose regimen

There is a report on a clinical study to examine the efficacy and safety of ABK in patients with pneumonia or sepsis caused by MRSA.[51] In this study, the target C_{peak} was initially set at 15–20 μg/mL and TDM was conducted. The efficacy rate was 87.5% (7/8 patients) for sepsis, 90.5% (19/21 patients) for pneumonia, and 89.7% (26/29 patients) in total (Table 3).

Based on the results, it was recommended that the dosage regimen of ABK should be initially set at 5–6 mg/kg or higher, and adjusted to achieve C_{peak} at 10–15 μg/mL or higher and C_{trough} lower than 2 μg/mL for treatment of patients with MRSA pneumonia or sepsis. With this strategy, low incidence of adverse drug reactions and higher clinical efficacy would be achieved. As for clinical effects, the efficacy rates for sepsis and pneumonia observed in this study were higher than the 70% efficacy rate which was observed in two other studies.[24,52] This high efficacy rate might be attributable to the higher concentration of ABK designed in this study. As the result of TDM intervention, the patients with higher C_{peak} at the final TDM than at the first TDM showed a 100% efficacy rate.

A study in elderly patients with pneumonia or sepsis caused by MRSA after once daily administration of ABK at the mean dose of 269.2 mg/day has been reported.[53] C_{peak} values for all patients, in whom ABK treatment had been

Table 3 Relationship between final daily dosage and efficacy/adverse drug reaction (ADR) rates

Final daily dosage (mg/kg)	Type of infection	n/29	Efficacy rate (%)** 89.7 (26/29)		Incidence of ADRs (%)* 17.2	(5/29)	Type of ADR
<5	Sepsis	1	0.0	(0/1)	100	(1/1)	Renal disorder, platelet count decreased
	Pneumonia	8	87.5	(7/8)	25.0	(2/8)	Renal disorder, constipation
	Total	9	77.8	(7/9)	33.3	(3/9)	
≥5 to <6	Sepsis	3	100	(3/3)	0.0	(0/3)	
	Pneumonia	5	80.0	(4/5)	20.0	(1/5)	Liver disorder
	Total	8	87.5	(7/8)	12.5	(1/8)	
≥6	Sepsis	4	100	(4/4)	0.0	(0/4)	
	Pneumonia	8	100	(8/8)	12.5	(1/8)	Elevated AST and ALT
	Total	12	100	(12/12)	8.3	(1/12)	

Notes: Eighty-nine patients from eleven clinical sites in Japan were enrolled in this clinical investigation, who in total were diagnosed with pneumonia or sepsis with MRSA infection or suspected MRSA infection. Among the patients, 29 adult patients who showed positive for MRSA detection following serum concentration analysis at the dose levels specified in the protocol were regarded as subjects for efficacy/safety analysis. Efficacy rate (%): (effective)/(effective + not effective) ×100. Incidence of ADRs (%): (number of patients with ADRs)/(total patients) ×100. *ADRs were observed in 5 patients. Incidence of ADRs was calculated by "5 patients/29 patients". **The efficacy of ABK were observed in 26 patients. The efficacy rate was calculated by "26 patients/29 patients".

Abbreviations: ABK, arbekacin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; MRSA, methicillin-resistant *Staphylococcus aureus*.

effective, were 15 µg/mL or higher. Their results and another report's results by Kimura et al[54] suggest that therapy at high doses of ABK is recommendable even in old people, but that the control of C_{trough} is crucial.

Combination therapy against multidrug-resistant Gram-negative bacteria

The combined effect of aminoglycosides and monobactams was studied using the Break-point Checkerboard Plate against MDRP.[55] Based on the result, a combination of AZT and ABK was selected as the anti-infective agent for MDRP treatment and the treatment result was reported. Since ABK also shows antibacterial activity against Gram-negative resistant bacteria, ABK as combination therapy can be used as a treatment option.

Adverse effect of ABK

Nephrotoxicity is a major adverse drug reaction to aminoglycoside antibiotics.[56–59] The incidence of renal-related adverse drug reactions after administration of ABK was related to C_{trough}. When C_{trough} was 1, 2 or 5 µg/mL, the estimated rate of adverse drug reactions were 2.5, 5.2, and 13.1% respectively, and the incidence of renal-related adverse drug reactions increased with a higher C_{trough}.[44] The incidence of ABK-induced nephrotoxicity was observed in all patients when ABK was administrated at a total dose of over 5,000 mg, while it was 4% at a total dose of less than 5,000 mg.[45]

It is supposed that ototoxicity of aminoglycoside occurs because of the gradual drug accumulation of endolymph and perilymph in the inner ear.[60–63] In addition, the results of some meta-analyses reported that there was no difference between single dosing and divided dosing in the incidence of ototoxicity.[64,65] Yamasoba et al reported that the cochlea could easily be damaged by aminoglycoside antibiotics because of mitochondrial point mutation at location 1555, and that hearing loss might occur with the administration of small amounts of aminoglycoside antibiotics.[66,67] This might suggest that hearing loss might occur in a patient who is not taking aminoglycoside antibiotics, but that the hearing loss is due to a familial or hereditary condition.

Conclusion

ABK has been used for the treatment of MRSA infections for over 20 years in Japan and about 15 years in Korea. Clinical evidence achieved in these two countries revealed the safety and efficacy of this drug. Since ABK shows good antibacterial activity against Gram-negative bacteria in addition to MRSA, some physicians reported the high efficacy of ABK for the treatment of multidrug-resistant Gram-negative bacterial infections such as *A. baumannii* and *P. aeruginosa*. Therefore, it is expected that ABK will be a good potential antibiotic as an additional treatment option, such as in combination with beta-lactams (eg, AZT), for serious infections due to its potent antibacterial activities against both MRSA and multidrug-resistant Gram-negative bacteria.

Disclosure

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