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Evaluation Of Efficacy Of Arbekacin In Drug-Resistant Bacterial Infections : A Study In a Tertiary Health Care Center Of South-East Region Of India

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ABSTRACT

Arbekacin (ABK) is a novel aminoglycoside, which has been used to treat severe infections, especially MRSA and multi-drug resistant gram-negative infections including strains resistant to gentamicin (GM), tobramycin (TOB), and amikacin (AMK). Many studies including the study by Hwang et al, found that Arbekacin was superior to vancomycin, and it could be a good alternative drug for vancomycin in methicillin-resistant Staphylococcus aureus (MRSA) treatment. This study was conducted to test the MDR Gram-negative isolates and the MRSA against Arbekacin by the E-test method.

MATERIALS & METHODS:

This prospective study was performed in the Department of Microbiology, Kalinga Institute of Medical Sciences, Bhubaneshwar, Odisha, India, for a period of 12 months between Jan2023 to Feb 2024. The study included all the MDR Gram-negative isolates and the MRSA isolates which were isolated from the routine clinical samples in the department. Each isolate was inoculated onto a Mueller-Hinton agar plate and was tested for Arbekacin sensitivity by the Arbekacin E-test strip and MIC was noted.

RESULTS:

Total 168 number of drug resistant bacteria were tested in this study. Among them 128 (76.2%) were Gram negative bacteria and 40 (23.8%) were Gram positive bacteria. Among the Gram negative bacteria *Klebsiella spp.* 18 (20%), Escherichia coli 4 (18.2%), Acinetobacter spp 3 (50%), Proteus spp. 3 (75%), Pseudomonas spp 4 (100%), Enterobacter spp. 2 (100%) were found to be sensitive to arbekacin. Among the Gram positive bacteria *Staphylococcus aureus* 22 (81.5%), *Coagulase negative Staphylococcus* 4 (100%), Enterococcus spp. 7 (77.8%) were found to be sensitive to arbekacin.

Conclusion

Since ABK shows good antibacterial activity against Gram-negative bacteria in addition to MRSA, it is recommended to use ABK for the treatment of multidrug-resistant bacterial infections. Therefore, it is expected that ABK will be a good potential antibiotic and also as an additional treatment option, such as in combination with other beta-lactams, for serious drug resistant bacterial infections.

KEYWORDS: Arbekacin (ABK), Aminoglycoside, MRSA.

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INTRODUCTION

Arbekacin (ABK) is a novel aminoglycoside, which has been used to treat severe infections, especially MRSA and multi-drug resistant gram-negative infections including strains resistant to gentamicin (GM), tobramycin (TOB), and amikacin (AMK). [1] Arbekacin acts by binding to both 50S and 30S ribosomal sub-units. Thus, it inhibits protein synthesis at bacterial ribosomes and causes codon misreading. Arbekacin is not inactivated by aminoglycoside-inactivating enzymes and shows concentration-dependent and long-lasting post-antibiotics effects. [2] ABK shows broad antimicrobial activities against not only Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) but also drug resistant strains of Gram-negative bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* etc.[3]

Many studies including the study by Hwang et al, found that Arbekacin was non-inferior to vancomycin, and it could be a good alternative drug for vancomycin in methicillin-resistant Staphylococcus aureus (MRSA) treatment. [4] Another analysis by Hamado et al showed that Gram-negative bacteria (GNB) that were inhibited by low minimal inhibitory concentrations (MICs) of amikacin (AMK) or gentamycin (GM) were eradicated by the end of the ABK treatment. [5]

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 Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring decided to develop a clinical practice guideline for TDM of ABK for the following reasons. [6] First, although the daily dose of 150–200 mg was approved in Japan, recent PK-PD studies revealed that higher serum concentration is

required to achieve better clinical efficacy and several findings concerning the usefulness of higher dosage regimen have obtained recently. [7] Second, although maximal concentrations that obtained immediately after the end of administration (C_{max}) was generally adopted, the serum concentration at 1 h after initiation of administration [peak serum concentration (C_{peak})] proved to be more suitable as an efficacy indicator of aminoglycosides. [8] Lastly, as ABK is approved only in Japan, no international practice guideline for TDM has not been available in ABK to date. [9,10]

AIM OF THE STUDY

This study was conducted to test the MDR Gram-negative isolates and the MRSA against Arbekacin by the E-test method.

MATERIALS & METHODS

This prospective study was performed in the Department of Microbiology, Kalinga Institute of Medical Sciences, Bhubaneshwar, Odisha, India, for a period of 12 months between Jan2023 to Feb 2024. The study included all the MDR Gram-negative isolates and the MRSA isolates which were isolated from the routine clinical samples in the department.

MICROBIOLOGICAL METHODS

Each of the isolate was sub cultured onto nutrient agar slopes. The Arbekacin E-test strip was first tested with control strain of Escherichia coli and Staphylococcus aureus from the stock culture. After controls strains were satisfactory (MIC <4), the test isolates were inoculated. Standard American type culture collection (ATCC) control strains within acceptable limits were used as quality control strains for Arbekacin testing, E. coli ATCC 25922, Staphylococcus aureus ATCC 29213, P. aeruginosa ATCC 27853.

Then each isolate was inoculated onto a Mueller-Hinton agar plate and was tested for Arbekacin sensitivity by the Arbekacin E-test strip to observe the MIC (minimum inhibitory concentration). The MIC was noted in the observation notebook. When the MIC was found to be less than 4 mcg/ml , isolate is sensitive; MIC >4 mcg/ml and <8mcg/ml is intermediate and >8mcg/ml is resistant.

ETHICS

The study was approved by the Institutional review board and ethics committee of Kalinga Institute of Medical Sciences, Bhubaneshwar, Odisha, India. A written or oral informed consent was not obtained by the patients whose isolates were included in this study due to the non-interventional study design and this consent procedure was approved by the ethics committee of our institution.

RESULTS

Total 168 number of drug resistant bacteria tested in this study. Among them 128 (76.2%) were Gram negative bacteria and 40 (23.8%) were Gram positive bacteria. Among the Gram negative bacteria *Klebsiella spp.* 18 (20%), Escherichia coli 4 (18.2%), Acinetobacter spp 3 (50%), Proteus spp. 3 (75%), Pseudomonas spp 4 (100%), Enterobacter spp. 2 (100%) were found to be sensitive to arbekacin. Among the Gram positive bacteria *Staphylococcus aureus* 22 (81.5%), *Coagulase negative Staphylococcus* 4 (100%), Enterococcus spp. 7 (77.8%) were found to be sensitive to arbekacin.

Table 1: Distribution of Gram-negative bacteria

Organism isolated (Total 168)				
Gram negative bacteria (n= 128)				
	SENSITIVE	**RESISTANT**	**INTERMIDIATE**	**Total**
Klebsiella spp.	18 (20%)	70 (77.8%)	2 (2.2%)	90
Escherichia coli	4 (18.2%)	16 (77.7%)	2 (0.09%)	22
Acinetobacter spp.	3 (50%)	2 (33.3%)	1 (16.7%)	6
Proteus spp.	3 (75%)	1 (25%)	0	4
Pseudomonas spp.	4 (100%)	0	0	4
Enterobacter spp.	2 (100%)	0	0	2

In table 1, Klebsiella spp. shows a high resistance rate (77.8%) compared to its sensitivity rate (20%). This indicates that Klebsiella spp. may be difficult to treat with standard antibiotics, and resistance is a significant concern for this species. Escherichia coli has a similar resistance pattern to Klebsiella, with a high resistance rate (72.7%) and a low sensitivity rate (18.2%). This suggests that this strain of E. coli is also problematic in terms of treatment efficacy. Acinetobacter spp. shows a more balanced profile with a higher percentage of sensitive isolates (50%) compared to the other bacteria. The resistance rate is lower (33.3%), and there is also a notable intermediate rate (16.7%). Proteus spp. demonstrates the highest sensitivity rate (75%) among the listed bacteria and has a low resistance rate (25%). There are no intermediate cases, suggesting that Proteus spp. is more likely to respond well to treatment compared to others. Pseudomonas spp. shows an excellent sensitivity profile with no resistant or intermediate isolates. This suggests that, in this dataset, Pseudomonas spp. is fully sensitive to the antibiotics tested. Enterobacter spp. also exhibits a perfect sensitivity profile with no resistant or intermediate isolates. This indicates that this particular strain of Enterobacter is very responsive to the antibiotics used in this study.

High Resistance: Klebsiella spp. and Escherichia coli have notably high resistance rates, indicating challenges in treating infections caused by these bacteria. Moderate Sensitivity: Acinetobacter spp. and Proteus spp. have higher sensitivity rates, suggesting better outcomes with treatment compared to the higher resistance strains. Excellent Sensitivity: Pseudomonas spp. and Enterobacter spp. show complete sensitivity, which is promising for treatment effectiveness in these cases.

Table 2: Distribution of Gram positive bacteria(n=40)

	SENSITIVE	RESISTANT	INTERMIDIAT	
Staphylococcus aureus	22 (81.5)	4 (14.8%)	1 (3.7%)	27
Coagulase negative	4 (100%)	0	0	4
Enterococcus	7 (77.8%)	2 (22.2%)	0	9

In table 2, Staphylococcus aureus demonstrates a high sensitivity rate (81.5%) with a relatively low resistance rate (14.8%). The intermediate rate is also low (3.7%). This suggests that most strains of Staphylococcus aureus in this dataset are responsive to the antibiotics tested, although there is some level of resistance. Coagulase-negative staphylococcus shows a perfect sensitivity profile with no resistant or intermediate cases. This indicates that all tested strains of coagulase-negative staphylococci are fully sensitive to the antibiotics. Enterococcus has a high sensitivity rate (77.8%) with a lower resistance rate (22.2%). The absence of intermediate cases suggests that the strains are either fully sensitive or resistant to the antibiotics tested.

High Sensitivity: Staphylococcus aureus and Coagulase-negative staphylococcus both show high sensitivity rates, with Coagulase-negative staphylococcus having a perfect sensitivity profile. This indicates effective treatment options for these bacteria. Moderate Sensitivity: Enterococcus has a slightly lower sensitivity rate compared to Staphylococcus aureus but still shows a good overall sensitivity profile. Low Resistance: Resistance is relatively low across the board, particularly in Coagulase-negative staphylococcus, where no resistance is observed.

Overall, the data suggests that the Gram-positive bacteria in this dataset are generally responsive to the antibiotics tested, with Coagulase-negative staphylococcus showing the most favorable sensitivity profile.

DISCUSSION

Arbekacin (ABK) (Meiji Seika Pharma Co, Ltd, Tokyo, Japan) has the hydroxy amino-butyryl group as its chemical structure and is classified as a kanamycin family aminoglycoside. [10] 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). [11] 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 to treat sepsis and pneumonia caused by MRSA. In addition, Habekacin has also been used in Korea since 2000. [12]

ABK showed strong antimicrobial activity against Gram-positive bacteria such as *S. aureus*3 and *Staphylococcus epidermidis*. [13] Antibacterial activities of ABK, GM, TOB, and AMK against 54 methicillin-susceptible *S. aureus* clinical isolates were determined. [13] 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. [14] 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). [15] ABK also has superior antibacterial activity against Gram-negative bacteria including *Pseudomonas aeruginosa*. [16]

A study by Matsumoto et al shows that the initial dose of ABK should be at 5–6 mg/kg or higher and the dosage regimen should be adjusted to achieve C_{peak} at 10–15 μg/mL or higher in the treatment of patients with pneumonia or sepsis caused by MRSA. This strategy would surely achieve low incidence of adverse events while obtaining high clinical efficacy. [10]

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. [17] 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. [18]

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).The cumulative percentage of MIC against MRSA with the antimicrobial susceptibility surveillance conducted in Japan. [19] The antimicrobial activity of ABK was more potent than the other anti-MRSA drugs except daptomycin.

CONCLUSION

Since ABK shows good antibacterial activity against Gram-negative bacteria in addition to MRSA, it is recommended to use ABK for the treatment of multidrug-resistant bacterial infections. Therefore, it is expected that ABK will be a good potential antibiotic and also as an additional treatment option, such as in combination with other beta-lactams, for serious drug resistant bacterial infections.

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