

The usefulness of arbekacin compared to vancomycin

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Abstract The bacteriological efficacy response (improved, arbekacin vs. vancomycin; 71.2% vs. 79.5%) and clinical efficacy response (improved, arbekacin vs. vancomycin; 65.3% vs. 76.1%) were not statistically different between the two groups. The complication rate was significantly higher in the vancomycin group (32.9%) compared to the arbekacin group (15.1%) ($p=0.019$). Arbekacin was not inferior to vancomycin, and it could be a good alternative drug for vancomycin in methicillin-resistant *Staphylococcus aureus* (MRSA) treatment.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is frequently resistant to the majority of commonly used

antimicrobial agents, including beta-lactam antibiotics, aminoglycosides, macrolides, chloramphenicol, tetracycline, and fluoroquinolones [1]. The prevalence of methicillin resistance is known to be more than ~60–70% among *S. aureus* isolates from hospitals in Korea [2, 3]. MRSA has become a one of the most important causes of nosocomial pathogenic infections, and the use of vancomycin for the treatment of MRSA infection has increased [4]. Unfortunately, vancomycin-resistant *Enterococcus* (VRE) and vancomycin-resistant coagulase-negative *Staphylococcus* (VRCNS) have been reported, as well as vancomycin-resistant *S. aureus* (VRSA) [5–7]. To prevent the spread of VRE, VRCNS, and VRSA, the use of vancomycin has to be reduced. This will require the introduction of a new class of antibiotics that can replace vancomycin [8].

Arbekacin is an antibacterial agent and belongs to the aminoglycoside family of antibiotics. It was introduced to treat MRSA infection. Pharmacokinetic advantages such as concentration-dependant bactericidal activity and prolonged post-antibiotic effect are more appreciable than vancomycin [9]. However, only a few reports of clinical data describing this new kind of antibiotic exist outside of Japan, which was the first country that approved its use against MRSA infections [10]. Therefore, presently, MRSA infection is treated mainly with vancomycin and teicoplanin, which are glycopeptide antibiotics.

We studied the clinical and bacteriological efficacy and safety of arbekacin compared to vancomycin in the treatment of infections caused by MRSA.

Method

This was a retrospective case–control study of patients who were admitted to Chonbuk National University Hospital, a

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Table 1 General characteristics of the study population

	Arbekacin (n=73)	Vancomycin (n=73)	p-value
Age (years)	54.1±16.4	56.3±14.7	0.397
Sex			
Male	43 (58.9%)	43 (58.9%)	1.000
Female	30 (41.1%)	30 (41.1%)	
Department			
Medical	15 (20.5%)	38 (52.1%)	<0.001
Surgical	58 (79.5%)	35 (47.9%)	
Clinical status			
Sepsis	5 (6.8%)	6 (8.2%)	0.063
Wound- and catheter-related	45 (61.6%)	31 (42.5%)	
Others ^a	23 (31.5%)	36 (49.3%)	
Medication duration (days)	19.4±15.7	18.2±11.3	0.608

^aOtitis media (13), meningitis (6), pneumonia (29), peritonitis (6), urinary tract infection (UTI), cellulitis, neutropenic fever (1)

Analyzed by the *t*-test and the Chi-squared test

1,100-bed tertiary care university hospital in Jeonju, Korea, from January 1st, 2009 to May 31st, 2010, and received the antibiotics arbekacin or vancomycin. All of the MRSA-infected patients who received arbekacin were enrolled during the study period. The vancomycin group infected by MRSA was selected by age and sex that matched the arbekacin group. The study protocol was approved by the Institutional Review Board of Chonbuk National University Hospital.

In this study, nephrotoxicity was defined as when at least 50% reduction was seen in the glomerular filtration rate (GFR) using the abbreviated modified diet in the renal disease (MDRD) equation, which was $GFR (mL/min/1.73 m^2) = 186 P_{cr}^{-1.154} \times age^{-0.203} \times (1.212 \text{ if black}) \times (0.742 \text{ if female})$ [11]. Hepatotoxicity was defined as when the aspartate aminotransferase/alanine aminotransferase (ALT/AST) levels were raised over two times the baseline values during treatment. Leukocytopenia was defined as a continuous decrease lower than $4.8 \times 10^3/\mu L$ in the number of white blood cells found in the complete blood cell count during

treatment. Drug fever was defined as a disorder characterized by fever coinciding with the administration of a drug and disappearing after the discontinuation of the drug [12].

The bacteriological efficacy response (BER) was classified with improved and failure. The improved BER was defined as no growth of MRSA, whereas failure was defined as the growth of MRSA culture at the end of therapy or during treatment. The clinical efficacy response (CER) was classified as improved and failure. Improved CER was defined as resolution or reduction of the majority of signs and symptoms related to the original infection. Failure was defined as no resolution and no reduction of the majority of the signs and symptoms, or the worsening of one or more signs and symptoms, or new symptoms or signs associated with the original infection or a new infection [13].

Categorical variables were compared by the Chi-squared test and continuous variables were compared by the unpaired *t*-test. SPSS software (version 15.0) was used throughout and *p*-values of less than 0.05 were considered to be statistically significant.

Table 2 Safety and outcomes in patients receiving arbekacin or vancomycin

	Arbekacin (n=73)	Vancomycin (n=73)	p-value
Complications			
No	62 (84.9%)	49 (67.1%)	0.019
Yes	11 (15.1%)	24 (32.9%)	
Nephrotoxicity	5 (6.8%)	6 (8.2%)	0.754
Leukopenia	4 (5.5%)	5 (6.8%)	0.731
Hepatotoxicity	3 (4.1%)	3 (4.1%)	1.000
Skin rash	0 (0.0%)	5 (6.8%)	N/A
Drug fever	0 (0.0%)	6 (8.2%)	N/A
Outcomes			
BER			
Improved	52 (71.2%)	58 (79.5%)	0.249
Failure	21 (28.8%)	15 (20.5%)	
CER			
Improved	47 (65.3%)	54 (76.1%)	0.157
Failure	25 (34.7%)	17 (23.9%)	

N/A, not applicable; BER, bacteriological efficacy response; CER, clinical efficacy response
Analyzed by the Chi-squared test

Results

A total of 146 patients were enrolled in this study. Seventy-three patients receiving arbekacin were compared with the same number of patients receiving vancomycin (Table 1). The mean age of the arbekacin group was 54.1 ± 16.4 years, and that of the vancomycin group was 56.3 ± 14.7 years. There was no gender difference between the two groups. The arbekacin group was more common in surgical section than the vancomycin group ($p < 0.001$). The clinical status ($p = 0.063$) or the medication duration (19.4 ± 15.7 days vs. 18.2 ± 11.3 days) was not different between the two groups.

The complications of the antibiotics between the two groups were different (Table 2). The complication rate was significantly higher in the vancomycin group (32.9%) than in the arbekacin group (15.1%) ($p = 0.019$). However, individual complications such as nephrotoxicity, leukopenia, and hepatotoxicity were not significantly different between the two groups. Skin rash and drug fever occurred only among patients in the vancomycin group. In the outcome section, the BER (improved, arbekacin vs. vancomycin; 71.2% vs. 79.5%) and the CER (improved, arbekacin vs. vancomycin; 65.3% vs. 76.1%) were not statistically different between the two groups (Table 2).

Discussion

In this study, arbekacin had a similar efficacy to vancomycin in patients with MRSA. In addition, the side effects in the arbekacin group were significantly lower than in the vancomycin group. This showed that arbekacin may be a good alternative drug for the treatment of infectious disease with MRSA. Furthermore, this could lead to the decrease of vancomycin usage in hospitals and decrease antibiotic-resistant microorganisms, particularly VRE and vancomycin-intermediate *S. aureus* (VISA), in clinical settings.

Approximately 80% of *S. aureus* strains isolated in intensive care units (ICUs) are resistant to methicillin in Asia [14]. More than 60% of MRSA were found in central line-associated bloodstream infections in ICUs from the United States [15]. Glycopeptides such as vancomycin and teicoplanin are still the most frequently chosen antibiotics for the treatment of MRSA infections, but the susceptibility to vancomycin diminished in MRSA strains [16]. In addition, VRSA strains have emerged in clinical settings [17]. Although VRSA infections continue to be rare and no transmission has been identified, it remains a serious public health concern all over the world. It was shown that, with more vancomycin exposure, there was a higher risk for VRSA or VRE [17]. Prudent use of vancomycin as well as the development of alternative therapeutic options against MRSA is, therefore, required.

Arbekacin, a derivative of the aminoglycoside dibekacin, has been reported to have good in vitro activity against MRSA [18, 19]. Previous reports showed that the majority of MRSA isolates in Europe and Japan were susceptible to arbekacin [20]. Arbekacin has been used for the treatment of MRSA infections is shown to be as useful as vancomycin based on clinical data [21, 22]. Lee et al. showed that arbekacin-based combination regimens could be an alternative option for glycopeptides in the treatment of MRSA or hetero-VISA infection [19]. In this study, arbekacin was not different to vancomycin in clinical trials. This shows that arbekacin could be a good alternative drug for glycopeptides.

The major side effects of vancomycin include local phlebitis, fever, neutropenia, skin rash, and renal toxicity [23]. The major side effects of arbekacin were renal and ear toxicity, like other aminoglycosides [18]. In this study, individual side effects of the antibiotics were not different between the two groups. However, arbekacin had fewer side effects than vancomycin overall.

There were several limitations in this study. First, it was a retrospective case–control study. Second, the two groups were not balanced at the clinical department. Surgical patients had a higher representation in the arbekacin group. However, the clinical status was not different between the two groups.

In conclusion, arbekacin was not inferior to vancomycin. We suggest that arbekacin could be a good alternative drug for vancomycin in MRSA treatment in the hospital. More well-designed studies are required in order to evaluate the exact clinical response between arbekacin and vancomycin.

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