

In Vitro Activity of Arbekacin and Fosfomycin Against Methicillin-Resistant *Staphylococcus aureus* Clinical Isolates at Siriraj Hospital

Suwanna Trakulsomboon, Ph.D.,
Visanu Thamlikitkul, M.D.

ABSTRACT

In vitro activity of arbekacin and fosfomycin against 103 strains of methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from different patients hospitalized at Siriraj Hospital, Bangkok, Thailand from 2006 to 2008 was determined by Kirby-Bauer disk diffusion method. The rates of susceptibility of MRSA to arbekacin and fosfomycin were 89.3 and 81.6 percent, respectively. The susceptibility of MRSA to arbekacin or fosfomycin was 94.2 percent. Arbekacin and fosfomycin may be alternative antibiotics for therapy of MRSA infections if the MRSA strains are susceptible. (*J Infect Dis Antimicrob Agents* 2009;26:11-7.)

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most common bacteria causing infections in hospitalized patients at Siriraj Hospital, Bangkok, Thailand.^{1,2} The prevalence of MRSA was found to be 41.5 percent of all strains of *S. aureus* isolated from hospitalized patients at Siriraj Hospital between January and May 2005. Therefore, the empirical treatment of hospitalized patients suspected of having *S. aureus* infection at Siriraj Hospital should include an anti-MRSA agent since the prevalence of MRSA is greater than 10 percent.³ The conventional

agent for therapy of MRSA infections is vancomycin. However, there are several limitations of treatment of MRSA infections with vancomycin, and its role in the management of serious infections is being reconsidered.⁴ Vancomycin treatment failure is associated with an increase in the minimal inhibitory concentration (MIC) as well as a decrease in the rate of bacterial killing. The intrinsic limitations of vancomycin also include a poor tissue penetration particularly in the lung, a relatively slow bacterial killing, and a potential for toxicity. Therefore, a search for alternative agents effective against MRSA is needed.

Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

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Reprint request: Visanu Thamlikitkul, M.D., Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

E-mail : sivth@mahidol.ac.th

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Arbekacin is an aminoglycoside which is a derivative of dideoxykanamycin B (dibekacin) with activities against both Gram-positive and Gram-negative bacteria.⁵ Arbekacin is stable in the presence of aminoglycoside-modifying enzymes produced by MRSA, and it is an effective aminoglycoside antibacterial against MRSA.⁶⁻⁸ Arbekacin will be available in Thailand shortly.

Fosfomycin, a phosphonic acid derivative, has a unique bactericidal activity. It inhibits uridine diphosphate-N-acetyl-glucosamine enol-pyruvyl-transferase, an enzyme catalyzing the bacterial cell membrane transportation of the substrate for cell-wall synthesis of bacteria. Glycerophosphate and glucose-6-phosphate active transport bacterial system is necessary for the action of fosfomycin to achieve membrane lysis of the targeted pathogen, while minimizing the possibility of cross resistance with other antibacterials.⁹ Fosfomycin has been available in Thailand for a decade.

The objective of our study was to determine the *in vitro* activity of arbekacin and fosfomycin against MRSA isolated from patients hospitalized at Siriraj Hospital, a medical school, Bangkok, Thailand.

MATERIALS AND METHODS

Bacterial isolates

One hundred and three strains of MRSA isolated from different infected patients hospitalized at Siriraj Hospital, Bangkok, Thailand, from 2006 to 2008 were

included. These were isolated from the lower respiratory tract (43 isolates), pus (36 isolates), blood (23 isolates), and urine (1 isolate). All isolates had oxacillin MIC of >4 mg/L and vancomycin MIC of <4 mg/L.

Susceptibility testing

The activity of arbekacin and fosfomycin against the studied organisms was determined by Kirby-Bauer disk diffusion method. The arbekacin disk (30 µg, Eiken Chemical Co. Ltd., Japan) and fosfomycin disk (50 µg, Oxoid Co. Ltd., Thailand) were used. The quality control was performed by testing the susceptibility of *S. aureus* ATCC 25923. The methodology for susceptibility testing was by direct colony suspension as recommended by the Clinical and Laboratory Standards Institute (CLSI).¹⁰ The test isolate was grown overnight onto blood agar at 35°C, and then the colonies were picked up and suspended in sterile normal saline equivalent to a 0.5 McFarland standard. The suspension was used to inoculate onto Mueller-Hinton agar, and the antibacterial disk was placed according to the manufacturer's recommendations. The agar plate was incubated at 35°C for 16-18 hours before the inhibition zone diameters were read. The interpretative criteria for susceptibility of *S. aureus* to arbekacin and fosfomycin are shown in Table 1.

RESULTS

The inhibition zone diameters of arbekacin and fosfomycin against the quality control organism *S.*

Table 1. Interpretative criteria for susceptibility of *Staphylococcus aureus* to arbekacin and fosfomycin.

Antimicrobial	Disk content	Resistance	Intermediate	Susceptible
Arbekacin	30 µg (potency)	< 13 mm	14-17 mm	> 18 mm
Fosfomycin	50 µg (potency)	< 13 mm	14-17 mm	> 20 mm

aureus ATCC 25923 were 18 and 30 mm, respectively. The distribution of the inhibition zone diameters of arbekacin and fosfomycin against the MRSA strains are shown in Tables 2 and 3 as well as Figures 1 and 2. The rates of susceptibility of MRSA to arbekacin and fosfomycin were 89.3 and 81.6 percent, respectively. The susceptibility of MRSA to either arbekacin or fosfomycin was 94.2 percent.

DISCUSSION

Arbekacin is stable in the presence of amino-

glycoside-modifying enzymes produced by MRSA, and it is an effective aminoglycoside antibacterial against MRSA.⁵⁻⁸ Arbekacin was reported to be effective in the treatment of MRSA infections, and it has been widely used in Japan for the treatment of MRSA infections.¹¹⁻¹⁹ The recommended dosage of arbekacin is 3-4 mg/kg per day.

Fosfomycin was found to be active against *S. aureus* including MRSA.²⁰⁻²⁵ Fosfomycin was given to patients on primary intention or according to the susceptibility testing results or after failure of the

Table 2. The distribution of inhibition zone diameters of arbekacin against 103 isolates of methicillin-resistant *Staphylococcus aureus*.

Inhibition zone diameter (mm)	Number (%) of the isolate
10	1 (1)
13	1 (1)
15	3 (2.9)
16	5 (4.9)
17	1 (1)
18	21 (20.4)
19	6 (5.8)
20	33 (32)
21	4 (3.9)
22	10 (9.7)
23	8 (7.8)
25	6 (5.8)
27	2 (1.9)
28	2 (1.9)

Table 3. The distribution of inhibition zone diameters of fosfomycin against 103 isolates of methicillin-resistant *Staphylococcus aureus*.

Inhibition zone diameter (mm)	Number (%) of the isolate
6	16 (15.5)
14	1 (1)
15	2 (1.9)
20	3 (2.9)
22	2 (1.9)
23	4 (3.9)
25	20 (19.4)
26	2 (1.9)
27	6 (5.8)
28	6 (5.8)
30	25 (24.3)
31	1 (1.1)
32	1 (1.1)
33	3 (2.9)
35	9 (8.7)
36	2 (1.9)

previously administered antibiotics to achieve resolution of the infection.⁹ Fosfomycin disodium was administered intravenously (1-24 g daily, administered in divided doses every 6-8 hours) for a maximum of 60 days; in the majority of cases, it was administered in combination with other antibacterials (ceftriaxone, cefotaxime, cefoperazone, aztreonam, sulbactam, vancomycin, rifampin, ciprofloxacin, gentamicin, and

amikacin). The most common Gram-positive and Gram-negative etiologic pathogens were *S. aureus* and *P. aeruginosa*, respectively. A resolution of infection was achieved in 77.6 percent to 88.2 percent. A low rate of adverse events, mainly associated with the gastrointestinal tract and the skin as well as a pain at the injection site, was reported. Fosfomycin had synergistic in vitro activity and

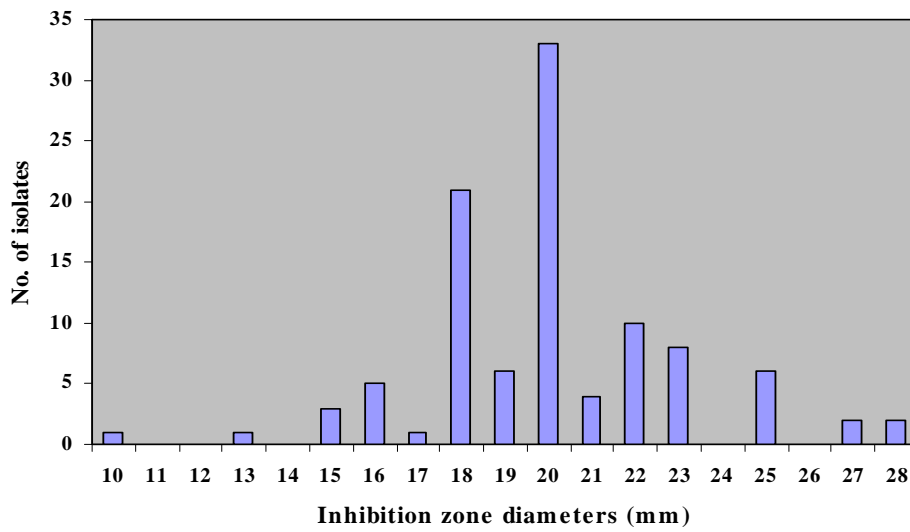


Figure 1. The distribution of inhibition zone diameters of arbekacin against 103 isolates of methicillin-resistant *Staphylococcus aureus*.

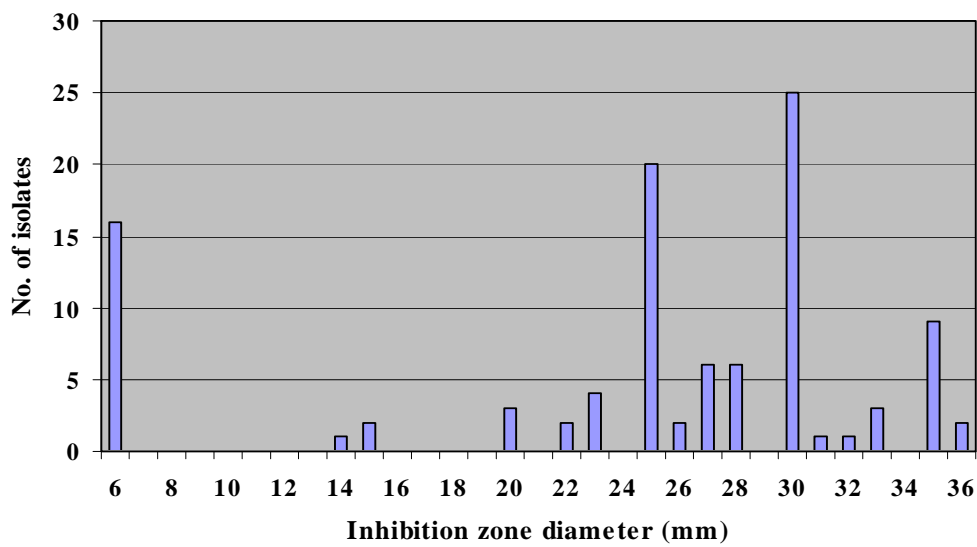


Figure 2. The distribution of inhibition zone diameters of fosfomycin against 103 isolates of methicillin-resistant *Staphylococcus aureus*.

synergistic effect on a MRSA-induced biofilm in a rat model with arbekacin.^{26,27} A combination of arbekacin and fosfomycin was effective for the treatment of MRSA infections.²⁸ Fosfomycin was also synergistic against *S. aureus* with other antibacterials including vancomycin, teicoplanin, pefloxacin, netilmicin, amikacin, cefazolin, imipenem, cefoperazone/sulbactam, linezolid, quinupristin/

dalfopristin, and such combinations might prevent fosfomycin resistance during therapy.²⁹⁻³⁴

Based on the aforementioned reports and our in vitro activity of arbekacin and fosfomycin against MRSA isolated from hospitalized patients at Siriraj Hospital, arbekacin and fosfomycin may be alternative agents for the therapy of MRSA infections if the MRSA strains are susceptible to arbekacin and fosfomycin.

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