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RESEARCH ARTICLE

Daptomycin and tigecycline susceptibility of vancomycin resistant enterococci isolated from rectal swab cultures

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ABSTRACT

Objective: Vancomycin resistant enterococci (VRE) are important healthcare associated multidrug resistant organisms because of their easily spread in the hospital environment, difficulty to cure and high mortality rate. The aim of this study was to evaluate in vitro activity of daptomycin and tigecycline against VRE strains isolated from rectal swab samples of hospitalized patients.

Methods: Sixty non-duplicate VRE strains isolated from rectal swabs of hospitalized patients between October 2010 and February 2013 at Ankara Training and Research Hospital were included into the study. Ankara Training and Research Hospital in Ankara in Turkey is a 600-bed, tertiary care, teaching hospital. Minimum inhibitory concentration (MIC) values of daptomycin and tigecycline were determined by E-test method (bioMerieux, France).

Results: All of the strains were susceptible to daptomycin, three of them (5%) were resistant to tigecycline. MIC_{50} and MIC_{90} values of daptomycin were 1.5 µg/ml and 2 µgr/ml, and of tigecycline were 0.64 µg/ml and 0.125 µg/ml, respectively.

Conclusion: As a result; all of the strains were susceptible to daptomycin. On the other hand, resistance to tigecycline was exhibited by 5% of VRE isolates. Clinicians should be aware of the possibility of the emergence of tigecycline non-susceptibility and should closely monitor tigecycline MICs of enterococci. *J Microbiol Infect Dis 2014; 4(3): 107-110*

Key words: VRE, daptomycin, tigecycline, susceptibility

Rektal sürüntü kültürlerinden izole edilen vankomisin dirençli enterokok suşlarının daptomisin ve tigesiklin duyarlılıkları

ÖZET

Amaç: Hastane ortamında kolay yayılımı, infeksiyonlarının tedavisinin zor ve mortalite oranlarının yüksek olması nedeni ile çoklu ilaca dirençli vankomisin dirençli enterokoklar (VRE) önemli organizmalardır. Bu çalışmanın amacı; yatan hastalardan alınan rektal sürüntü örneklerinden izole edilen VRE suşlarında in vitro daptomisin ve tigesiklin duyarlılığını belirlemektir.

Yöntemler: Çalışmaya Ekim 2010- Şubat 2013 tarihleri arasında Ankara Eğitim ve Araştırma Hastanesinde yatan hastaların rektal sürüntülerinden izole edilen 60 VRE suşu dahil edildi. Ankara Eğitim ve Araştırma hastanesi 600 yataklı 3. basamak bir araştırma hastanesidir. Daptomisin ve tigesiklin için minimum inhibitor konsantrasyon (MIK) değerleri E-test yöntemi (bioMerieux, Fransa) ile belirlendi.

Bulgular: Tüm suşlar daptomisine duyarlı olup; üçü (%5) tigesikline dirençli saptandı. Daptomisin için MIK50 ve MIK90 değerleri sırasıyla 1.5 µgr/ml ve 2 µgr/ml saptanırken tigesiklin için 0.064 µg/ml ve 0.125 µg/ml olarak saptandı.

Sonuç: Sonuç olarak; tüm suşlar daptomisine duyarlı saptandı. Diğer yandan VRE izolatlarında tigesiklin direnci %5 olarak saptandı. Klinisyenler enterokoklarda tigesiklin direncine karşı dikkatli olmalı ve tigesiklin MIK değerini yakından takip etmelidir.

Anahtar kelimeler: VRE, daptomisin, tigesiklin, duyarlılık

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INTRODUCTION

Antimicrobial drug resistance is a growing public health problem, and multidrug-resistant pathogens such as vancomycin resistant enterococci (VRE) are increasing worldwide, with the increased consumption of glycopeptides. The limited therapeutic options currently available for the treatment of VRE infections emphasize the need for new antimicrobial agents with activity against these pathogens and for ongoing efforts to limit the transmission of VRE in health care settings.[1,2] The clinical importance of the genus *Enterococcus* is directly related to its antibiotic resistance, which contributes to the risk of colonization and infection.[3] However, colonizations are far more frequent than infections.[4] Daptomycin and tigecycline are effective in the treatment of infections related to gram positive bacteria.[5,6] Daptomycin, a cyclic lipopeptide produced by *Streptomyces roseosporus*, approved for the treatment of complicated skin and soft-tissue infections and *Staphylococcus aureus* bloodstream infection, is the only antibiotic with in vitro bactericidal activity against VRE that is approved by the Food and Drug Administration (FDA).[7] Daptomycin exhibits a lower potency against enterococci than staphylococci.[8,9] Tigecycline, the first member of a new class of broad-spectrum antibiotics, the glycylcyclines was licensed for the parenteral treatment of adult patients with complicated intra-abdominal infections and complicated skin and soft tissue infections.[10] Tigecycline is highly active against Gram-positive pathogens, including methicillin resistant *S. aureus* (MRSA), methicillin resistant *S. epidermidis* (MRSE) and vancomycin susceptible and resistant enterococci.[11,12] The aim of this study was to evaluate the in vitro activity of daptomycin and tigecycline against VRE isolates.

METHODS

This study performed at a 600 bed tertiary care hospital which has an infection control commitee. In the period from October 2010 to February 2013, 60 non-duplicated vancomycin resistant *Enterococcus faecalis* and *Enterococcus faecium* strains were isolated from rectal swab cultures from patients intensive care units and various clinics in our hospital. The isolates were stored at -20°C in brain heart infusion broth, suplemented with glycerol, before testing. The isolates were grown overnight on sheep blood agar at 37°C for 24 h and were tested for ampicillin, erithromycin, vancomycin, teicoplanin and linezolid. Suspension of the isolates in 0.5 McFarland was prepared and inoculated on to Mueller Hinton agar plates. The testing of the antimicrobial susceptibilities to the ampicillin, erythromycin, vancomycin, teicoplanin and linezolid were carried out on Mueller Hinton agar by the Kirby Bauer disc diffusion method. Susceptibilities of the strains to daptomycin and tigecycline were performed using the E-test (bioMerieux, France) according to the recommendations of the CLSI 2011 and the manufacturer. The MIC breakpoints used for susceptibility for daptomycin and tigecycline were taken as ≤ 4 µg/ml and ≤0.5 µg/ml, respectively, as approved by the FDA.[8,13] *E. faecalis* ATCC 29212 was used as a control strain in the study.

RESULTS

Among 60 enterococcal isolates, 22 (36.7%), 28 (46.7%), 1 (1.7%) and 9 (15.0%) were isolated in 2010, 2011, 2012 and 2013, respectively. Thirty eight strains (63.0%) were isolated from intensive care units and 22 (37%) from internal medicine clinics (Figure 1). All of the strains were resistant to ampicillin, erythromycin, vancomycin, teicoplanin but susceptible to linezolid. Daptomycin MIC values of strains were determined between 0.125 and 4 µgr/ml; all of them were susceptible. MIC_{50} and MIC_{90} values of daptomycin was 1.5 µgr/ml and 2 µgr/ml, respectively. Tigecycline MIC values of the strains were determined between 0.023 and 0.75 µg/ml; 3 of the strains having MIC ≥ 0,5 µg/ml were resistant to tigecycline. MIC_{50} and MIC_{90} values of tigecycline were 0.064 µg/ml and 0.125 µg/ml, respectively (Table 1).

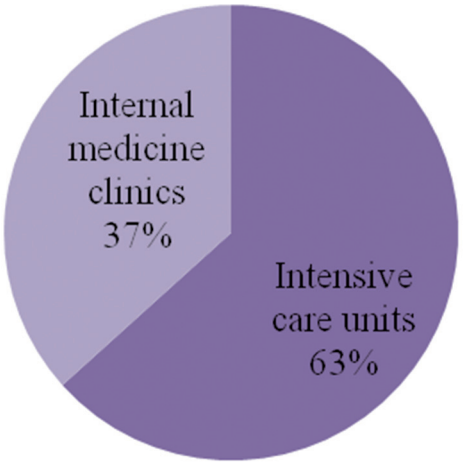

Figure 1. Distribution of rectal swab samples to clinics

Table 1. MIC_{50} and MIC_{90} (µg/mL) values for daptomycin and tigecycline of VRE strains.

MIC (µg/mL)				
	MIC_{50}	MIC_{90}	MIC Range	Susceptibility %
Daptomycin	1,5	2	0,125-3	100%
Tigecycline	0,064	0,125	0,023-0,75	95%

MIC: Minimum inhibitory concentration, VRE: Vancomycin resistant enterococ

DISCUSSION

Vancomycin had been used since 1950s, but the emergence of resistance of *Enterococcus species* was not reported until 1988 in the United Kingdom and France. Incremental vancomycin usage for MRSA infection may explain the timing.[14] Since VRE was first isolated in Turkey from nosocomial infection in 1998 at Akdeniz University Hospital, the incidence of antimicrobial-resistant bacteria has continuously increased with the rising consumption of antibiotics.[15]

Daptomycin, a new lipopeptide antibiotic, is highly bactericidal against the majority of gram-positive human pathogens, including MRSA and VRE. Its mechanism of action is unique resulting in the destruction of the membrane potential without lysis of the cell wall.[16] Tigecycline, the first semisynthetic glycylcycline available for clinical application, is a novel 9-t-*butyl*-substituted minocycline derivative that overcomes several major tetracycline resistance mechanisms. It demonstrates broad-spectrum antimicrobial effects against multiple resistant gram-positive, gram-negative, anaerobic, and atypical pathogens.[17] Sader et al.[18] evaluated the in vitro activity of daptomycin and comparators tested against clinical isolates from European hospitals over a 7-year period (2003-2009); 7241 consecutive *Enterococcus spp.* (9.4% VRE) isolates were collected in 34 medical centers located in 13 European countries, Turkey and Israel. All *E. faecalis* strains were susceptible to daptomycin (MIC_{50}: 2 µg/ml, MIC_{90}: 2 µg/ml, 100% susceptible). In this study, daptomycin and linezolid were the most active agents tested against VRE. Aktaş et al.19 evaluated the in vitro activity of daptomycin against 118 VRE strains by broth dilution method and all of the strains susceptible to daptomycin (MIC_{50}:1 µg/ml, MIC_{90}: 2 µg/ml) and MIC range was 0.125-2 µg/ml. At a tertiary care hospital in Turkey, all 31 enterococcal strains, 4 of which were VRE, were found to be susceptible to daptomycin by E-test method and MIC range was 0.094-2 µg/ml.[20] In another study in a tertiary care hospital in Turkey, all 52 enterococcal strains in which resistance to vancomycin were not investigated, were found to be susceptible to daptomycin.[21] Similar to these results, in our study, all of 60 VRE strains were susceptible to daptomycin; MIC_{50} was 1.5 µg/ml, MIC_{90} 2 µg/ml. Chitnis et al.22 evaluated 50 VRE strains, 20 were from clinical samples and 30 were from rectal swabs from newborns in Central Indian hospital. All of them were susceptible to daptomycin. Among these VRE isolates, MIC for daptomycin was 0.19-1.5 µg/ml except two isolates which had MIC of 3 µg/ml. Non-susceptibility of enterococci to daptomycin (MIC>4 µg/ml by broth dilution and E-test) remains infrequent, with an overall prevalence of 0.6% among clinical isolates in a recent series.[7] It is declared that the resistance of daptomycin in *E. faecium* is between 0.5% and 1.5% worldwide.[23] Kamboj et al.[24] examined the daptomycin susceptibility profile of all isolates collected during episodes of VRE bacteremia at a cancer center in New York between 2007-2009. One hundred seventy six patients had VRE bacteremia, including 18 (10.2%) with bacteremia due to daptomycin resistant VRE strains; resistance rates were increased significantly, from 3.4% in 2007 to 15.2% in 2009.

Sader et al.[25] monitored the in vitro activity of tigecycline in 2011 for continued potency worldwide. A total of 22.005 gram positive and gram negative isolates were consecutively collected in North America, Europe, Latin America and Asia Pacific Region and tested for susceptibility according to the broth microdilution method. Of the VRE isolates 99% were susceptible to tigecycline. Jones et al.[26] studied resistance patterns of 218 Latin American enterococcal isolates. VRE rate was 14% but all of them were susceptible to tigecycline and daptomycin. Chen et al.[27] evaluated in vitro activity of tigecycline to 219 vancomycin resistant *E. faecium* isolates collected during the period from 2006 to 2010. Among these strains 98.6% were susceptible to tigecycline (MIC_{50}: 0.03 µg/ml, MIC_{90}: 0.125 µg/ml) and MIC range was 0.016-1 µg/ml. Karaoğlan et al.[28] monitored in vitro activity of tigecycline in 60 enterococcal strains from Turkey (57 *E. faecium* and 3 *E. gallinorum*) by E-test method; all of them susceptible to tigecycline (MIC_{50}: 0.125 µg/ml, MIC_{90}: 0.5 µg/ml) and MIC range was 0.094-1 µg/ml. Of our 60 VRE isolates, three of them (5%) were resistant to tigecycline. Our resistant rate to tigecycline was higher than the other studies. The limitatiton of our study is that the subtyping was not performed. It would be better if we could have identified *E. spe-*

cies as *E. faecium* or *E. faecalis*. It is known that *E. faecium* isolates are more resistant than *E. faecalis* isolates.[4]

Conclusion

As a conclusion; all of the strains were susceptible to daptomycin, so this agent can be used at the treatment of VRE. Resistance to tigecycline was exhibited by 5% of VRE isolates. We think that clinicians should be aware of the possibility of the emergence of tigecycline nonsusceptibility and should closely monitor tigecycline MICs of enterococcal strains.

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