



Determination of In Vitro Activity of Linezolid in Resistance Gram-positive Bacteria by E-Test Method

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Abstract

Introduction: The incidence of infections caused by multidrug-resistant Gram-positive bacteria is increasing in the past years. The pathogens such as glycopeptid-resistant *enterococci*, methicillin-resistant *Staphylococcus aureus* (MRSA), and coagulase-negative staphylococci (CoNS) have emerged widely and they contribute an increase. The treatment of the patients infected with the multidrug-resistant pathogens is extremely difficult. The aim of this study was to determine in vitro susceptibility of vancomycin-resistant *enterococci* (VRE) and staphylococci against linezolid that may provide new alternative to treat.

Methods: A total of 80 isolates of staphylococci (30 MRSA, 30 MSSA, and 20 Methicillin-resistant coagulase-negative staphylococci [MRCoNS]) obtained from various clinical specimens and 20 VRE isolates recovered from blood and rectal swab specimens were sent to our microbiology laboratory. Linezolid susceptibility was determined by disc diffusion methods and E-test for all isolates. In addition, for all isolates, sensitivity to other antibacterials was detected by Kirby–Bauer disc diffusion method according to guidelines established by the Clinical and Laboratory Standards Institute.

Results: The results showed that all strains were fully susceptible to linezolid (minimal inhibitory concentration [MIC] ≤2 µg/ml). The linezolid effectiveness is not different between the MRSA and MSSA strains. MICs were changed for MRSA from 0.018 to 2 µg/ml, MSSA from 0.25 to 1.5 µg/ml, and MRCoNS from 0.19 to 1 µg/ml. MICs were changed from 0.38 to 2 µg/ml for VRE strains.

Discussion and Conclusion: As a result of the present study, it was decided that linezolid appears to be a good alternative in the treatment of infections caused by Gram-positive bacteria, especially those resistant to glycopeptides or with reduced sensitivity.

Keywords: E-test; in vitro activity; linezolid; resistance.

The course of infectious diseases has changed greatly since the beginning of antibiotic age in the 1940s. Previously, multiple antibiotic resistance and treatment problems seen with Gram-negative bacteria were also observed in the treatment of Gram-positive bacterial infections in later years

[1]. In addition to the treatment difficulty caused by multiple antibiotic resistance in infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) strains, these strains can cause nosocomial epidemics, making MRSA infections a serious health problem all over the world.

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Submitted Date (Başvuru Tarihi): 04.06.2018 **Accepted Date (Kabul Tarihi):** 03.08.2018

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These epidemics bring with it a huge financial burden [2–4]. In 2002, the first vancomycin-resistant *Staphylococcus aureus* (VRSA) strain was isolated in the US and was followed by new ones. Frequent use of vancomycin in severe infections caused a decreased sensitivity to and resistance to vancomycin [5].

Glycopeptide resistance has increased significantly in recent years. In our hospital, an increase in the number of patients with or without glycopeptide-resistant *enterococci* (GRE) is being observed [6]. As a result, varying resistance patterns require alternative treatment options for vancomycin. The latest antibiotics developed to treat resistant Gram-positive microorganisms include oxazolidinones. Oxazolidinones are new synthetic antimicrobials found in 1987, and the first member of this group is linezolid [7].

The aim of our study is to determine the in vitro activity and minimal inhibitory concentration (MIC) of linezolid, which was introduced in our country in 2005 against infections caused by staphylococci and *enterococci* isolated from blood cultures and various clinical samples. We tried to determine whether linezolid activity is different for methicillin-resistant and sensitive strains.

Materials and Methods

This study is a prospective study that was approved by the Ethics Committee of Haydarpaşa Numune Education and Research Hospital. A total of 100 strains, including 30 MRSA, 30 MSSA, 20 methicillin-resistant coagulase-negative staphylococci (MRCoNS), and 20 vancomycin-resistant *enterococci* (VRE) strains, isolated from various clinical samples were studied. Fifteen VRE strains were isolated from blood cultures and 5 from fecal swabs. The samples from which these strains were isolated are shown in Table 1. Isolated strains were identified, passaged in stock culture media, and stored at -70°C until the study was performed.

Identification of the Bacteria

Staphylococci

The strains grown in hemoculture were passaged into the blood agar medium, and their pure cultures were obtained and stained with gram dye. Morphology of bacterial colonies and hemolysis of the strains were evaluated. Catalase-positive strains were tested for the presence of coagulase.

Methicillin resistance was evaluated in all staphylococcus strains. For this purpose, Müller-Hinton agar with 2% NaCl was used. It was prepared from the 24-h culture of the staphylococci to be investigated in suspension with McFarland 0.5 turbidity in the broth.

This suspension was cultured on the medium. Standard 1 µg oxacillin discs were used to determine the methicillin resistance. After 24 h of incubation at 35°C , the inhibition zones were measured and evaluated according to the Clinical and Laboratory Standards Institute (CLSI) criteria. If diameters of oxacillin zone were ≥ 13 mm, 11–12 mm, and \leq , then *S. aureus* was considered to be susceptible, less susceptible, and resistant to oxacillin, while MRSA with inhibition zones of ≥ 18 and ≤ 17 mm was deemed to be susceptible and resistant to oxacillin, respectively. In addition, susceptibilities of all strains were determined by Kirby–Bauer disk diffusion method against antibiotics as indicated in the CLSI guidelines.

Enterococci

If the catalase test was negative for the bacteria isolated from the culture samples, bacterial growth in 6.5% NaCl and PYR test was applied. The strains grown in 6.5% NaCl and yield PYR test positivity were evaluated as *enterococci*.

6.5% NaCl Assay

For this assay, 2–3 colonies of bacteria were seeded on brain heart infusion (BHI) broth containing 6.5% NaCl. The

Table 1. Microorganisms isolated material

Microorganism	Microorganisms isolated material								
	Serum	BOS	Abscess	Tracheal Aspirate	Peritoneal fluid	The joint fluid	Catheter	Gaita	Total number
MRSA	24	3	1	1	1	0	0	0	30
MSSA	22	0	3	1	2	1	1	0	30
MR-CoNS	19	1	0	0	0	0	0	0	20
VRE	15	0	0	0	0	0	0	5	20

MRSA: Methicillin-resistant *Staphylococcus aureus*; MSSA: Methicillin-Susceptible *Staphylococcus aureus*; MR-CoNS: Methicillin-resistant coagulase-negative staphylococci; VRE: Vancomycin-resistant enterococci.

development of turbidity as a result of bacterial growth was considered test positivity.

Vancomycin powder was added onto the BHI agar to determine vancomycin resistance with a vancomycin concentration of 6 mg/l. *Enterococci* strains were cultivated on this medium at decreasing dilutions. At the end of incubation, the strains were evaluated as VRE. Bile esculin agar was used for the isolation of VREs from feces. The strains were immunized with BHI agar (VRE agar) containing vancomycin 6 µg/ml, and vancomycin resistance was determined.

Kirby–Bauer disk diffusion method was used for antibiotic susceptibility of the strains. Vancomycin, penicillin, ampicillin, cefazolin, erythromycin, levofloxacin, and linezolid discs were used. ATCC 25923 strain for staphylococci and ATCC 29212 strain for *enterococci* were used as control strains.

Results

In our study, the rates of resistance in MRSA strains determined by disk diffusion method were 100% for erythromycin, 57% for clindamycin, 27% for fusidic acid, 30% for sulfamethoxazole, 93% for ciprofloxacin, 90% for levofloxacin, and 100% for gentamicin.

In the MSSA strains, resistance rates were found to be as indicated in parentheses: Erythromycin (30%), clindamycin (7%), fusidic acid (14%), SXT (17%), ciprofloxacin (10%), levofloxacin (10%), gentamicin (17%), penicillin and ampicillin resistance (100%), SAM (20%), and cefazolin (7%).

Resistance rates in MRCoNS strains were determined as follows: Erythromycin (60%), clindamycin (40%), fusidic acid (50%), SXT (60%), ciprofloxacin (90%), levofloxacin (70%), and gentamicin (50%).

Linezolid Results

Linezolid MICs were as follows: MRSA (0.018–2 µg/ml), MSSA (0.25–1.5 µg/ml), MRCoNS (0.19–1 µg/ml), and VRE (0.38–2 µg/ml) (Table 2).

Discussion

The incidence of multiple-resistant Gram-positive bacterial infections is increasing, and they complicate the treatment of nosocomial infections [1]. The high morbidity and mortality of MRSA infections led to the monitorization of the prevalence of multiple antibiotic-resistant staphylococci, mainly MRSA. Methicillin resistance rates have gradually increased within years, and in some centers, it reached up to 70% [8].

Due to methicillin resistance in Staphylococci, glycopeptide antibiotics are most effective, and reliable alternatives in cases seriously infected with these bacteria. Vancomycin is the leading glycopeptide antibiotic. Vancomycin can be widely used in empirical treatment of catheter-related infections in hemodialysis patients, as a prophylactic antibiotic in Gram-positive infections in patients who are receiving peritoneal dialysis, and in cardiovascular surgery patients who developed nosocomial infections due to MRSA. Due to its widespread use, the problem of resistance has started to emerge. While *S. aureus* has been found to have decreased susceptibility to vancomycin, since 2002, *S. aureus* strains have been reported to have high resistance to vancomycin (MIC >32 µg/ml) [9,10].

S. aureus strains with decreased susceptibility to glycopeptides (MIC 8–16–16 µg/ml) were first reported from Japan and then from the US, Europe, and Korea. These strains were found in patients who had been using vancomycin for long term without any recovery [1,11].

Teicoplanin, another glycopeptide preparation, has advantages such as ease of use and lesser side effects than vancomycin. Therefore, it was started to be used as the first option instead of vancomycin. Teicoplanin resistance develops more easily than vancomycin and has higher MICs.

Strains are susceptible to vancomycin, but decreased sensitivity to teicoplanin has been reported at an increased frequency [12,13]. Derbentli et al. [14] did not detect resistance to vancomycin in staphylococci strains, but a decreased rate of susceptibility was reported in 0.3%, and 0.8% of MRSA strains to vancomycin and teicoplanin, respectively.

Table 2. Linezolid MIC values in microorganisms

Microorganism	MIC values (µg/ml)													
n	2	1.5	1	0.75	0.5	0.38	0.25	0.19	0.125	0.094	0.064	0.047	0.018	Total
MRSA	1	-	2	9	6	4	3	1	2	-	-	1	1	30
MSSA	-	1	10	7	6	4	1	-	1	-	-	-	-	30
MRCoNS	-	-	2	5	10	1	1	1	-	-	-	-	-	20
VRE	6	3	3	2	3	3	-	-	-	-	-	-	-	20

MIC: Minimal inhibitory concentration; VRE: Vancomycin-resistant enterococci; MRCoNS: Methicillin-resistant coagulase-negative staphylococci.

The corresponding rates were reported as 0.4% and 1.3% in MRCoNS strains. In our study, vancomycin-resistant MRSA and MRCoNS strains were not detected.

As is seen herein, glycopeptide resistance is not seen as a common problem for our country. However, it is wise to seek alternative treatment options with non-glycopeptide antibiotics, especially, in patients treated with mild-to-moderate infections caused by MRSA. In such cases, susceptibility to other antibiotic groups such as fusidic acid, SXT, clindamycin, erythromycin, and quinolones is gaining importance. Fusidic acid has been in use beginning from 1962, and since 1998, it has an oral form in our country. Especially, fusidic acid activity in β -lactam antibiotic-resistant staphylococcal strains increased the interest in this antibiotic. Due to the availability of only its oral form, it has been found to be of use, especially, in the outpatient treatment of MRSA infections^[15]. In our study, fusidic acid sensitivity was found to be 73% in MRSAs, 86% in MSSAs, and 50% in MRCoNS. When the studies conducted on fusidic acid in our country are examined, in a study by Şengöz et al.^[16] performed with fusidic acid, the rates of resistance in MRSAs (9%), MSSAs (1%), MRCoNS (33%), and MSCoNS (21%) were detected as indicated. Doğan et al.^[17] reported that fusidic acid resistance was 11% in MSCoNS and 39% in MRCoNS strains isolated from blood samples. In our study, fusidic acid resistance was found to be higher in MRCoNS compared to other studies, but the susceptibility rates in MRSA and MSSAs were parallel to other studies.

These findings suggest that fusidic acid is an alternative antibiotic for the treatment of infections caused by methicillin-resistant staphylococci.

Another β -lactam antibiotic used in resistant staphylococci is SXT. Şengöz et al.^[16] showed that SXT sensitivity was 91% in MRSA, 95% in MSSA, 64% in MSCoNS, and 62% in MRCoNS strains. In another study, SXT sensitivity was found to be 92% in MRSAs and 20% in MRCoNS.^[18] In a study reported from India, SXT resistance in MRSA strains was found to be 63.2%.^[19] In our study, SXT sensitivity was found to be 70% in MRSAs, 83% in MSSAs, and 40% in MRCoNSs.

As seen in different studies, the sensitivity of SXT in staphylococci varies from center to center. Therefore, SXT is an antibiotic that can be used as an alternative to the geographical region where the infection develops. In our study area, it is considered to be an empirical antibiotic, especially in MSSA infections.

Quinolones are not among β -lactam group antibiotics, and some of their members are effective on staphylococci. In our study, resistance rates in MRSAs to ciprofloxacin and

levofloxacin were 93% and 90%, respectively. In MRCoNS, rates of resistance to ciprofloxacin and levofloxacin were similar (70%). In the study conducted by Şengöz et al.^[16] with MSSAs, the resistance to ofloxacin was 9%, while it was reported to be 84% in MRSAs and 67% in MRCoNSs. As seen here, resistance rates of quinolones in methicillin-resistant staphylococci are quite high, so they are not thought to be an alternative to empirical therapy in the treatment of infections with methicillin-resistant staphylococci.

In our study, erythromycin-sensitive strains were not detected in MRSAs, while erythromycin resistance was 30% in MSSAs and 60% in MRCoNSs. Rates of erythromycin resistance in MRSA strains in different studies from Turkey have been reported as 58.6%, 71%, 62%, 40.6%, and 75.6%, while, for MRCoNSs, these rates were indicated as 77% and 61%, respectively^[12,16]. In general, erythromycin is not considered as an alternative antibiotic for the treatment of methicillin-resistant staphylococci. Clindamycin is an alternative antibiotic for staphylococcal infections. In our study, clindamycin resistance was found in 57% of MRSA, 7% of MSSA, and 40% of MRCoNS strains. Clindamycin resistance has been reported as 39–54% in various studies performed in our country^[12,16].

In MRSAs, there is no susceptible strain against penicillin. In some studies, susceptible strains are reported to be negligible in MSSAs. In our study, in MRSA, MSSA, and MRCoNS resistance to penicillin, ampicillin was 100%, while ceftazolin resistance was 100% in MRSA and MRCoNS and 7% in MSSAs. Sulbactam-ampicillin resistance was found to be 100% in MRSA and MRCoNS and 20% in MSSA strains. In the study of Kanan et al.^[20], penicillin resistance was reported in 94% of MSSA and 100% in MRSA strains. As seen here, penicillin and ampicillin are not alternative antibiotics in the treatment of staphylococcal infections.

Enterococci have an important place among agents of nosocomial infections^[21]. Due to known intrinsic resistance of many *enterococci* to many antimicrobial agents, the number of antibiotics that can be used in the treatment of these agents is limited. The main antibiotics used in the treatment of enterococcal infections are penicillins, aminoglycosides, and glycopeptides^[22,23].

In recent years, there has been a problem in the treatment of *enterococci* due to the development of resistance to these antibiotics. VRE strains detected in *enterococci* in many countries have become widespread in our country in recent years. According to CDC data, a 25-fold increase in the prevalence of GRE between 1989 and 1993 was reported^[24]. Although *Enterococcus faecalis* is 4 times more

frequently encountered than *Enterococcus faecium* as an agent of infection, *E. faecium* is responsible for most GRE attacks. Between 1995 and 1997, vancomycin-resistant *E. faecalis* was found between 1.3% and 12.3% of the patients, while the incidence of vancomycin resistance in *E. faecium* strains increased from 28% to 52% [25].

In a study performed with the participation of 42 centers from 16 countries in 2004, 5.3% of a total of 719 Enterococcus strains were found to be resistant to vancomycin [26]. In our study, 15 of 20 VRE strains were isolated from clinical specimens and 5 of them from stool as a result of VRE surveillance. Linezolid sensitivity was found to be 100%.

The first member of the oxazolidinone group is linezolid. Due to their different mechanisms of action, they do not show cross-resistance with other antibiotics. In vitro linezolid resistance is difficult to develop. Development of resistance is typically due to a single nucleotide change in genes encoding 23 S ribosomal RNA. In a study conducted on 3770 Gram-positive strains with the participation of 25 hospitals in England in 2000, linezolid MIC was determined in strains of *S. aureus*, *E. faecalis*, and *Streptococcus pneumoniae*, and for all three bacterial strains, the MIC of linezolid was detected in the range of 1–4 µg/l. In the same study, while 4% of the strains were resistant to vancomycin, any linezolid-resistant strain was not detected [27]. In comparative studies with teicoplanin in the treatment of suspected and proven Gram-positive infections, linezolid was found to be more effective than teicoplanin in different disease categories [28].

A limited number of studies have been performed with linezolid in Turkey. Dizbay et al. [13] investigated linezolid sensitivity in 120 MRSA strains by disk diffusion method and no resistant strain was detected. In the study of Kanan et al. [20] the MIC ranges of linezolid were 1–4 µg/ml in MRSA, 0.5–2 µg/ml in MRCoNS 0.25–1 µg/ml, 1–2 µg/ml in *E. faecalis*, and 1–4 µg/ml in *E. faecium* Ertem et al. [29] did not report linezolid resistance between 2008 and 2009 in 120 hospital-acquired staphylococci strains. Ağalar et al. [30] found linezolid resistance as 3% in 276 staphylococci strains resistant to methicillin. In their study of 100 MRSA strains, Efe et al. [31] could not detect any resistance to linezolid. Cesur et al. [32] did not report resistant to linezolid, vancomycin, and teicoplanin in none of the 260 MRSA strains isolated from clinical specimens of patients hospitalized in ICUs of hospitals in seven cities of Turkey. In our study, the ranges of MIC for linezolid were determined in MRSA (0.018–2.0 µg/ml), MSSA (0.12–1.5–1 µg/ml), MRNNS (0.19–10.0 µg/ml), and VREs (2–0.38 µg/ml) as indicated.

As a result of all studies, it has been observed that linezolid is an important alternative in the treatment of resistant Gram-positive bacterial infections. Although the development of resistance to linezolid is not a problem at present, minimization of the development of resistance for the future should be targeted. To that end, it has been thought that rational use of antibiotics, cooperation between clinics, and regular surveillance are necessary.

Ethics Committee Approval: This study is a prospective study that was approved by the Ethics Committee of Haydarpaşa Numune Education and Research Hospital.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: S.C., N.C.; Design: S.K., S.A.; Data Collection or Processing: S.C., N.C.; Analysis or Interpretation: S.C., N.C., S.K.; Literature Search: S.C., S.K., G.K., S.Ö.; Writing: S.C.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study received no financial support.

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