Relationship Between Teicoplanin Use and Increase in Minimal Inhibitor Concentrations of Coagulase-Negative Staphylococci

Koagülaz Negatif Stafilokoklardaki Minimal İnhibitör Konsantrasyon Artışı ile Teikoplanin Kullanımı Arasındaki İlişki

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ABSTRACT

Aim: We aimed to determine the relationship between teicoplanin use and increased minimal inhibitor concentrations of coagulase-negative staphylococci (CNS) isolated from catheter related bloodstream infections (CRBSI) in patients with hematological malignancies.
Methods: The study was performed on CNS strains isolated from CRBSI of FN patients during the period between 2006-2010. Teicoplanin MICs were determined by using the Etest method. Demographic characteristics of patients, underlying hematological diseases, the dose and course of teicoplanin were recorded. Grams and international units of teicoplanin were further converted into defined daily doses (DDD).
Results: A total of 72 CNS strains causing CRBSI isolated from FN attacks of the patients were analyzed. Among them, *Staphylococcus. epidermidis* (47%) and *Staphylococcus haemolyticus* (42%) were the most frequent CNS species. Oxacillin resistance was detected in 74% of all isolates. Increase in MIC values among CNS strains were detected in 44 patients (61%). Mean MIC value for teicoplanin among CNS strains before the treatment was 2.1±1.76 µg/ml, and it was 4.4±3.89 µg/ml after the treatment (p<0.001). Increase in MIC was found to be significantly higher among oxacillin-resistant strains than oxacillin-susceptible strains (p=0,03). A positive correlation was determined between DDD of teicoplanin and MIC increase among CNS strains (p=0.06).
Conclusions: We detected an increase in teicoplanin MIC values of CNS isolated from catheter-related BSI related to teicoplanin consumption. The teicoplanin MIC increase was more prominent among oxacillin-resistant isolates. Teicoplanin should be used cautiously in the treatment of repeated CRBSI attacks caused by *S. epidermidis* and *S. haemolyticus* which occurred within 90 days after the previous attack.

Key Words: Teicoplanin, drug resistance, bacteremia, staphylococci, hematologic malignancy

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ÖZET

Amaç: Hematolojik maligniteli hastaların kateter ilişkili kan dolaşım infeksiyonlarından (KİKDİ) izole edilen Koagülaz negatif stafilokok (KNS)'lardaki Minimal inhibitör konsantrasyon (MİK) artışı ve teikoplanin kullanımı arasındaki ilişkiyi belirlemek amaçlanmıştır.
Gereç ve Yöntemler: Bu çalışma 2006-2010 yılları arasındaki KİKDİ olan febril nötropenik hastalardan izole edilen KNS suşlarında yapılmıştır. Teikoplanin MİK düzeyleri E-test® yöntemiyle belirlenmiştir. Hastaların demografik özellikleri, altta yatan hematolojik hastalıkları, teikoplanin doz ve süreleri kaydedilmiştir. Teikoplanin gramları ve uluslararası birimleri tanımlanmış günlük doza (DDD) çevrilmiştir.
Bulgular: Kateter ilişkili kan dolaşım enfeksiyonlu febril nötropenik hastalardan izole edilen toplam 72 KNS suşu incelenmiştir. En sık izole edilen KNS suşlarını *Staphylococcus epidermidis* 34(%47), *Staphylococcus haemolyticus* 30(%42) oluşturmuştur. Oksasilin direnci tüm izolatların %74'ünde saptanmıştır. Hastaların 44(%61)'ünde KNS suşlarının MİK değerlerinde artış saptanmıştır. Tedavi öncesi KNS suşları arasında Teikoplanin için MİK değeri 2.1±1.76 µg/ml, ve tedavi sonrası bu değer 4.4±3.89 µg/ml olarak saptanmıştır (p<0.001). MİK artışı oksasilin dirençli suşlarda, oksasilin duyarlı olanlara göre belirgin olarak yüksek olduğu saptanmıştır. Teikoplanin DDD dozu ile MİK artışı arasında pozitif korelasyon saptanmıştır (p=0.06).
Sonuçlar: Teikoplanin kullanımı ile KİKDİ'lerden izole edilen KNS suşlarında teikoplanin MİK değerinde artış saptanmıştır. Teikoplanin MİK artışı oksasilin dirençli suşlar arasında daha belirgindir. İlk atak 90 gün içinde oluşan *S. epidermidis* ve *S. haemolyticus* nedenli tekrarlayan kateter ilişkili kan dolaşım infeksiyonu tedavisinde teikoplanin dikkatli bir şekilde kullanılmalıdır.

Anahtar Sözcükler: Teikoplanin, ilaç direnci, bakteriyemi, stafilokok, hematolojik kanser

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INTRODUCTION

Catheter related bloodstream infections (CRBSI) caused by coagulase-negative staphylococci (CNS) are frequent in patients with febrile neutropenia (FN). Glycopeptides are used empirically in the treatment of these infections. Teicoplanin is preferred in the treatment of CRBSI in our center because of having less side effects and allowing for outpatient parenteral use. Recently, decreased susceptibility to teicoplanin among CNS has been reported, especially in *Staphylococcus haemolyticus* and *S. epidermidis*, due to the excessive use of glycopeptides (1,2,3). The treatment of CRBSI remains difficult, especially in febrile neutropenic patients infected with CNS, which has decreased susceptibility to teicoplanin. The increase in MIC levels of teicoplanin may cause treatment failure (4,5). Therefore, monitoring MIC levels of teicoplanin among CNS isolates is needed, especially in those isolated from repeated episodes.

In this study, we aimed to determine the relationship between teicoplanin use and increased minimal inhibitor concentrations of coagulase-negative staphylococci (CNS) isolated from CRBSI in patients with hematological malignancies.

METHODS

Approximately 1000 patients are admitted to Hematopoetic Stem Cell Transplantation (HSCT) and Hematology Unit per year. During the study period, between 2006-2010, the febrile neutropenic patients which developed CRBSI due to CNS, and received teicoplanin treatment were screened retrospectively. Following the inititaion of teicoplanin treatment, the patients which yielded CNS in blood cultures during the therapy course and or within 3 month after the discontinuation of therapy were included in the study. If CNS strains were yielded within 3 month from the same patients andwere identified as different type of CNS, these strains were excluded from the study.

Patient data were obtained from patient files using a database. Demographic characteristics of patients, underlying hematological diseases, the type of bone marrow transplantation, presence of central venous catheter, neutropenia, and the dose and course of teicoplanin were recorded. Grams and international units of teicoplanin were further converted into defined daily doses (DDD) (6). The DDD of teicoplanin was 400 mg for adult patients.

BBL Crystal ID kit Gram positive (Becton Dickinson, USA) were used for the identification of CNS. Susceptibility to oxacillin was tested by disk diffusion method. Teicoplanin MICs were determined by using E-test (AB Biodisk, Sweden) method. Microbiological procedures were performed according to Clinical Laboratory Standards Institute criteria (7). All strains were stored-at -70°C until the study was completed.

The statistical analysis of the data was performed using SPSS version 17.0 software package (SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed using the Chi-square or Fisher's exact test where appropriate. A univariate analysis was performed to explore the relationship between MIC levels of CNS and teicoplanin use.

RESULTS

A total of 231 CNS strains isolated from CRBSI of 124 patients with hematological malignancies were analyzed in the study. Only 72 of them met the criteria and were included in the study. Patient characteristics are shown in Table 1. Identification of strains revealed that *S. epidermidis* 34 (47%) and *S. haemolyticus* 30 (42%) were the most frequent CNS species. Other strains were *S. hominis* 4 (6%), *S. intermedius* 1 (1%), *S. capitis* 2(3%), and *S. saprophyticus* 1 (1%), respectively. Oxacillin resistance was detected in 74% of all isolates.

MIC_{50} and MIC_{90} values were 2 and 4 µg/ml among CNS strains before treatment (MIC range: 0.19-8 µg/ml), and 4 and 8 µg/ml after treatment (MIC range: 0.125-16 µg/ml). Increase in MIC values among CNS strains were detected in 60% of *S. haemolyticus*, and 64.7% of *S. epidermidis* isolates (totally 61%). Mean MIC value for teicoplanin among CNS strains before the treatment was 2.1±1.76 µg/ml while it was 4.4±3.89 µg/ml after the treatment ($p<0.001$) (Table 2). There was no correlation between MIC increase and the type of CNS. Increase in MIC was found to be significantly higher among oxacillin-resistant strains than oxacillin-susceptible strains ($p=0,03$).

A positive correlation was detected between DDD of teicoplanin and MIC increase among CNS strains, however it was not statistically significant ($p=0.06$). Age and gender of patients, the duration of neutropenia, the type of malignancy, duration of period after teicoplanin treatment were also not related to increases in MIC values ($p>0.05$).

Table 1. Characteristics of 72 patients with hematological malignancies in the study

Patient characteristics	Value
Female/male	27/45
Neutropenia	58 (80,6%)
Age	37,15±13.83 (16-64)
Type of bone marrow transplantation	46 (64%) (70% allogeneic)
Underlying diseases	*Number of patients*
Acute myeloid leukemia	26
Acute lymphoblastic leukemia	17
Multipl Myelom	14
Aplastic anemia	5
Hodgkin lymphoma	3
Non-hodgkin lymphoma	3
Chronic myeloid leukemi	4
Chronic lymphocytic leukemic	1
Myelodysplastic syndrome.	2
Thalassemia	1

DISCUSSION

Coagulase-negative staphylococci are the most common cause of catheter-related bloodstream infections (8). CNS has been reported as the most frequent Gram-positive organism isolated from BSI in patients with cancer in 33 US Hospitals (9). Besides the increase in the prevalence of CNS isolated from BSI, resistance rates to antimicrobials are also a major concern. They are more resistant to antimicrobial agents than other gram positive organisms. Recently, several studies have reported an increase in the prevalence of CNS with decreased susceptibility to glycopeptides (2,3). Although there are a few reports about decreased susceptibility to glycopeptides among CNS and teicoplanin consumption in the hospital, there is no report showingthe direct relationship between the use of glycopeptide antibiotics and increased MIC values. Therefore our results are the first to show the MIC increases with the teicoplanin use among CNS isolates. The MIC values of teicoplanin before treatment significantly increased during the 3-month period after the treatment.

Table 2. Comparison of MIC levels before and after treatment

All CNS isolates	Before treatment	After treatment	P value
MIC 50 (µg/ml)	2	4	-
MIC 90 (µg/ml)	4	8	
Mean MIC value	2.1±1.76	4.4±3.89	0.001
S. epidermidis	1.89±1.55	3.88±3.22	
S. hemolyticus	2.61±1.74	5.21±4.12	
Teicoplanin resistance, %	0	7	0.05

The MIC increase among the CNS isolate can cause a problem in clinical settings. Glycopeptide antibiotics are usually initiated empirically in the treatment of proven or suspected catheter-related BSI in febrile neutropenic patients. Inappropriateness of initial treatment is associated with increased mortality, morbidity, the length of hospital stay and the cost. It is estimated that the fatality rate of catheter-related bacteremia is 10–20% (10). According to our results, teicoplanin should be used cautiously in the treatment of BSI in patients who were treated with teicoplanin in the previous 3 months. If the blood cultures yielded CNS during the treatment of teicoplanin, the strains should be checked for the MIC increase through appropriate methods.

Patients with haematological malignancies are often managed with the aid of long-term tunnelled central venous catheters, such as Hickman lines (10). The presence of intravascular central lines in hematological patients was found to be related to the reduced susceptibility to teicoplanin, and resulted in poor clinical responses to teicoplanin therapy (4).

It may be due to biofilm production. de Allori et al. showed a significant association between biofilm production and resistance to a variety of antimicrobial agents among CNS strains, mainly *S. haemolyticus*, which was the species with the highest biofilm production and antimicrobial resistance. In that study, 42% of *S. haemolyticus*, and 40% of *S. epidermidis* strains assayed produced biofilms (11). It is important to detect biofilm-producing bacteria in order to implement an appropriate antimicrobial therapy at an early stage (11). We couldn't check our isolates for biofilm production, but it may be anticipated that they most likely produced biofilm because they wereisolated from catheter-related BSIs, and 89% of them were *S. haemolyticus* and *S. Epidermidis*.

Decreased susceptibility to teicoplanin is seen mostly among *S. haemolyticus* and *S. epidermidis* strains. Glycopeptide resistance may be due to changes in ultrastructural morphology, glycopeptide-binding capacity, membrane proteins, cell wall synthesis and composition (3). There are some reports about the increase of prevalence of CNS with decreased susceptibility to teicoplanin in some hospital settings (12). Del' Alamo et al. showed that the most frequent species was *S. epidermidis* (50.2%); however, the lowest rates of susceptibilities were shown by *S. haemolyticus* (4.2% to oxacillin and 70.8% to teicoplanin) (13). In our study, although MIC increase was seen in 61% of all isolates, there was no significant difference between the types of CNS. Similar to the results of the above study, teicoplanin MIC increase was detected more frequently among oxacillin-resistant strains. A positive correlation was found between the DDD of teicoplanin and MIC increase among CNS isolates, however it did not reach statistical significance. This may be due to a low number of CNS isolates in the study. Another limitation of the study is that a molecular identification was not performed among the CNS isolates, therefore, we cannot claim that the isolates which showed MIC increases are identical. In addition, the effect of MIC increases on the clinical success of teicoplanin was not evaluated in our study, and we need further studies to show that relationship.

CONCLUSION

Our results revealed that an increase in teicoplanin MIC values of CNS isolated from catheter-related BSI is related to teicoplanin consumption. The teicoplanin MIC increase was more prominent among oxacillin-resistant isolates. Teicoplanin should be used cautiously in the treatment of repeated catheter-related BSI attacks caused by *S. epidermidis* and *S. haemolyticus* which occurred within 90 days after a previous attack.

Conflict of Interest

No conflict of interest was declared by the authors.

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