Evaluation of the In vitro Activity of Ceftazidime-Avibactam and Ceftolozane-Tazobactam against Ceftazidime-Resistant *Pseudomonas aeruginosa* Isolates

Seftazidim-Avibactam ve Seftolozan-Tazobaktam'ın Seftazidim Dirençli *Pseudomonas aeruginosa* İzolatlarına Karşı İn vitro Aktivitesinin Değerlendirilmesi

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ABSTRACT

Introduction: This study aimed to assess the in vitro efficacy of ceftazidime/avibactam (CZA) and ceftolozane/tazobactam (C/T) against ceftazidime resistant *Pseudomonas aeruginosa* clinical isolates from Samsun Training and Research Hospital.

Materials and Methods: A total of 52 unique patient isolates of ceftazidime resistant *P. aeruginosa* were included in this study. Identification and antimicrobial susceptibilities of the strains were performed using a VITEK 2® automated system. The efficacy of CZA and C/T were determined by the gradient diffusion method (Liofilchem MIC strip test, Italy). We used the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines for Minimal Inhibitory Concentration interpretation.

Results: Among these 52 strains, 49 (94.2%) were susceptible to CZA and 51 (98.1%) to C/T. Both CZA and C/T had better activity than any one of the 3 anti-pseudomonal beta-lactams. Although the susceptibility rates of isolates to CZA and C/T were similar, according to MIC₅₀ values C/T (MIC₅₀ 1 µg/mL) was 2-fold more potent than CZA (MIC₅₀ 2 µg/mL).

Conclusion: CZA and C/T showed good activity against ceftazidime-resistant and/or carbapenem-resistant *P. aeruginosa* isolates and may serve as therapeutic options for infections caused by these organisms. However, further in vitro and in vivo studies are needed to assess the effectiveness of these new antimicrobials against multiple drug resistant *P. aeruginosa* isolates.

Key Words: Ceftazidime-resistant *Pseudomonas aeruginosa*; Carbapenem-resistant *Pseudomonas aeruginosa*; Ceftazidime-avibactam; Ceftolozane-tazobactam

ÖZ

Seftazidim-Avibactam ve Seftolozan-Tazobaktam'ın Seftazidim Dirençli *Pseudomonas aeruginosa* İzolatlarına Karşı İn vitro Aktivitesinin Değerlendirilmesi

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Giriş: Bu çalışmada, Samsun Eğitim ve Araştırma Hastanesi'nde seftazidim dirençli *Pseudomonas aeruginosa* klinik izolatlarına karşı seftazidim/avibactam (CZA) ve seftolozan/tazobaktam (C/T)'in in vitro duyarlılıklarının değerlendirilmesi amaçlanmıştır.

Materyal ve Metod: Seftazidim dirençli 52 *P. aeruginosa* hasta izolatu çalışmaya dahil edildi. Suşların tanımlaması ve antimikrobiyal duyarlılıkları VITEK 2® otomatize sistemi ile çalışıldı. CZA ve C/T etkinliği gradiyent strip test ile (Liofilchem MIC strip test, İtalya) tespit edildi. Minimal İnhibitör Konsantrasyon yorumu Avrupa Antimikrobiyal Duyarlılık Testi (EUCAST) kılavuzlarına göre yapıldı.

Bulgular: Bu 52 suştan 49 (%94.2)'u CZA'ya ve 51 (%98.1)'i C/T'ye duyarlı olarak saptandı. Hem CZA hem de C/T, 3 anti-psödomonal beta-laktam antibiyotiklerin herhangi birinden daha iyi aktiviteye sahipti. İzolatların CZA ve C/T'ye duyarlılık oranları benzer olmasına rağmen, MIC₅₀ değerlerine göre C/T (MIC₅₀ 1 µg/mL), CZA'dan (MIC₅₀ 2 µg/mL) iki kat daha etkiliydi.

Sonuç: CZA ve C/T, seftazidim dirençli ve/veya karbapenem dirençli *P. aeruginosa* izolatlarına karşı iyi aktivite göstermiştir ve bu organizmaların neden olduğu enfeksiyonlar için terapötik seçenekler olarak tercih edilebilirler. Ancak bu yeni antimikrobiyallerin çoklu ilaca dirençli *P. aeruginosa*'ya karşı etkinliğini değerlendirmek için daha fazla in vitro ve in vivo çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Seftazidim dirençli *Pseudomonas aeruginosa*; Karbapenem dirençli *Pseudomonas aeruginosa*; Seftazidim-avibactam; Seftolozan-tazobaktam

INTRODUCTION

Pseudomonas aeruginosa is a non-fermentative gram-negative bacillus that causes a wide range of serious clinical infections, including hospital-acquired pneumonia, ventilator-associated pneumonia (VAP), bacteremia, urinary tract infections and skin infections^[1]. It is the greatest cause of nosocomial infections and is responsible for ~10% of all hospital-acquired infections worldwide. Also, it rarely affects healthy individuals, but causes high morbidity and mortality in immunocompromised individuals and especially in cystic fibrosis (CF) patients^[2].

P. aeruginosa is difficult to treat with currently available antibiotics^[3]. Additionally, the World Health Organization (WHO) has recently listed carbapenem-resistant *P. aeruginosa* as one of three bacterial species in which there is a critical need for the development of new antibiotics to treat infections^[4]. *P. aeruginosa* displays resistance to a variety of antibiotics, including β-lactams, quinolones, and aminoglycosides. Generally, the major mechanisms can be classified into intrinsic, acquired, and adaptive resistance^[5].

Development of new antibiotics or alternative therapeutic strategies are urgently required because conventional antibiotic therapies against *P. aeruginosa* infections have become increasingly ineffective due to the rise of multidrug-resistant strains^[6]. Ceftolozane-tazobactam (C/T) and ceftazidime-avibactam (CZA) are two newer betalactam-beta-lactamase inhibitor combinations with broad-spectrum activity against Gram-negative bacteria, including MDR *P. aeruginosa*^[7]. In late 2014/early 2015, U.S. Food and Drug Administration (FDA) approved both antimicrobial agents for the treatment of complicated urinary tract infections and complicated intra-abdominal infections caused by *P. aeruginosa*^[8].

Limited data exists regarding the comparative activity of CZA and C/T against ceftazidime-resistant *P. aeruginosa* isolates in Turkey. In this study, it was aimed to evaluate the in vitro activity of CZA and C/T against ceftazidime resistance *P. aeruginosa* clinical isolates recovered from in a tertiary hospital in Turkey and to compare the activity of CZA, C/T and anti-pseudomonal beta-lactam antibiotics (piperacillin-tazobactam,

cefepime, imipenem, meropenem) against these isolates.

MATERIALS and METHODS

Bacterial Isolates

A total of 52 non-duplicate ceftazidime resistance *P. aeruginosa* clinical isolates from Samsun Training and Research Hospital were included in the study. All isolates were recovered between 2018 and 2019. All clinical samples sent to laboratory were cultured on sheep blood agar and eosin methylene blue agar. After 24-48 hours of incubation, species-level identification and antibiotic sensitivity analyses of the isolates were performed using a VITEK 2 automated system (Biomérieux, France). The clinical sources of the isolates and patient data were obtained retrospectively from the hospital automated records system. All isolates were stored at -80°C in skim milk and sub-cultured twice onto 5% sheep's blood agar prior to testing. *P. aeruginosa* ATCC 27853 was used as quality control.

Antimicrobial Susceptibility Testing

MICs of CZA and C/T were determined by MIC test strips (Liofilchem, Italy). Firstly, a 0.5 McFarland turbidity standard suspension of each isolate was spread onto Mueller-Hinton agar (BD, USA). The surface of the plate was allowed to dry for 15 min before applying the MIC test strip. After the application of the MIC test strip, plates were incubated at 35°C in ambient air. The MIC results were interpreted according to Clinical and Laboratory Standards Institute (CLSI) criteria in M100-S28 as well as European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint tables (version 9.0)^[9,10]. Both CLSI and EUCAST have defined CZA MIC breakpoints for *P. aeruginosa* as follows: ≤8 mg/mL (susceptible) and ≥16 mg/mL (resistant). The CLSI has defined C/T MIC breakpoints for *P. aeruginosa* as ≤4 mg/mL (susceptible), 8 mg/mL (intermediate) and ≥16 mg/mL (resistant), while EUCAST has defined C/T MIC breakpoints as ≤4 mg/mL (susceptible) and ≥8 mg/mL (resistant).

Multidrug-resistance (MDR) was defined as resistance to at least three of the following: antipseudomonal cephalosporin, piperacillin-tazobactam, meropenem, ciprofloxacin and aminogly-

coside^[11]. Strains sensitive to only colistin and/or aminoglycoside were considered to be extensively drug resistant (XDR)^[12].

The study was approved by the Ethics Commission of Samsun Training and Research Hospital SBÜSEAH-KAEK-2020/2/5.

Statistical Analysis

Data were analyzed using SPSS software (version 17, SPSS Inc. Chicago, IL). Pearson Chi-Square test was used to compare categorical variables.

RESULTS

A total of 52 clinical isolates of *P. aeruginosa*, only one specimen per site per patient, was considered in this study. *P. aeruginosa* strains were isolated from patients in the intensive care unit (n= 23), internal sciences clinics and surgical sciences clinics of our hospital. The clinical sources of the isolates included 14 tracheal aspirate (27%), 12 urine (23%), 12 wound (23%), 11 sputum (21%), 1 blood, 1 drain and 1 sterile body fluid (2%) samples. The origin of clinical samples tested in this study is detailed in Table 1.

All isolates (n= 52) were resistant to ceftazidime (MIC range= 8-64 mg/mL) according to CLSI breakpoints. Among these isolates, 88.5% (46 of 52) were resistant to ceftazidime and cefepime; 86.5% (45 of 52) were resistant to ceftazidime and piperacillin-tazobactam, 75% (39 of 52) were resistant to three traditional anti-pseudomonal β-lactam agents according to both CLSI and EUCAST criteria. 10 (19.3%) isolates were sensitive to only colistin and/or aminoglycoside were considered to be XDR and 42 (80.7%) isolates were considered to be MDR.

Among these 52 strains, 49 (94.2%) were susceptible to CZA and 51 (98.1%) to C/T (Table 2). Among the 52 ceftazidime-resistant *P. aeruginosa* isolates; 26 strains (50%) were resistant to MEM and/or imipenem. Among these 26 strains, the susceptibility rates to CZA and C/T were 92.3% (24/26) and 100% (26/26) respectively. Other antibiotic susceptibilities are shown in Table 2.

Figure 1 shows CZA and C/T MIC distributions for 52 ceftazidime resistant *P. aeruginosa*

Table 1. The origin of clinical samples (services and samples)

Sample	Intensive care	Internal medicine	Surgery clinics	Chest diseases	Dermatology	Total
Urine	3	6	3	0	0	12
Blood	1	0	0	0	0	1
Wound	5	3	3	0	1	12
Sputum	4	2	0	5	0	11
Endotracheal aspirat	13	0	0	1	0	14
Drain	0	0	1	0	0	1
Pleura	0	0	1	0	0	1
Total	26	11	8	6	1	52

Table 2. In vitro activities of CZA and C/T and susceptibility profile to other antibacterial afor the 52 ceftazidime-resistant and/or carbapenem-resistant *P. aeruginosa* isolates

Organism group/antimicrobial agent	MIC range (mg/L)	MIC ₅₀	MIC ₉₀	Susceptibility no, (%)
<i>P. aeruginosa</i> CAZ-R				
CZA	0.50-32	2	4	49/52 (94.2)
C/T	0.12-8	1	2	51/52 (98.1)
Cefepime				6/52 (11.5)
Piperacillin tazobactam				7/52 (13.5)
Imipenem				27/52 (51.9)
Meropenem				28/52 (53.8)
Ciprofloxacin				29/52 (55.8)
Levofloxacin				32/52 (61.5)
Amicasin				47/52 (90.4)
Gentamycin				39/52 (75)
Colistin				52/52 (100)
<i>P. aeruginosa</i> CAZ-R + IMI and/or MER-R				
CZA	1-32	2	4	24/26 (92.3)
C/T	0.19-4	0.75	1.5	26/26 (100)
Cefepime				2/26 (7.6)
Piperacillin tazobactam				2/26 (7.6)
Ciprofloxacin				11/26 (42.3)
Levofloxacin				12/26 (46.1)
Amicasin				24/26 (92.3)
Gentamycin				
Colistin				19/26 (73) 26/26 (100)

isolates. Among 52 isolates, two isolates were resistant to CZA but susceptible to C/T and one isolate was resistant to both CZA and C/T according to EUCAST breakpoints but intermediate to C/T according to CLSI breakpoints. The MIC₅₀ values of CZA and C/T were 2 mg/mL and 1 mg/mL, respectively. Using MIC₅₀ values, C/T was two-fold more potent than CZA.

DISCUSSION

In recent years, it has been observed that in some geographical regions the prevalence of MDR and XDR *P. aeruginosa* strains has increased between 15% and 30%^[13,14]. One of the main consequences of multidrug resistance is the difficulty of selecting appropriate empirical antibiotic treatment. Patients with infections due to MDR/XDR pathogens are at an increased risk of receiving inadequate initial antimicrobial therapy^[15].

Especially the increase in carbapenem resistance among *P. aeruginosa* clinical isolates is worrisome because there has been little progress in the development of new antimicrobial agents targeting this organism^[16,17]. Although in vitro data show that colistin seems to be the most effective agent against resistant *P. aeruginosa* strains, its pharmacokinetic properties and nephrotoxicity limit its use in the treatment of these types of infections^[18].

Several in vitro studies have demonstrated that ceftazidime-avibactam and ceftolozane-tazobactam display good activity against MDR/XDR *P. aeruginosa* strains collected in different parts of the world with inhibition rates varying between 66.1% and 86.5% for CZA; 55% and 96.6% for C/T (19-22). There are only two studies from Turkey assessing the in vitro activity of CZA and C/T against clinical isolates of *P. aeruginosa*. In their study Mirza et al. have demonstrated susceptibility rates for CZA and C/T were 83.3% and 82.4%, respectively against 102 meropenem-non-susceptible *P. aeruginosa* isolates^[23]. The other study was conducted by Aydemir et al., and in their study, susceptibility rates against CZA and C/T in MDR and XDR *P. aeruginosa* strains have been found as 78.2% and 68.8%, respectively^[24]. In our study, susceptible rates for CZA and C/T were 94.2% and 98.1%, against

CAZ resistant *P. aeruginosa* strains; 92.3% and 100% against 26 CAZ-R + IMI and/or MER-R *P. aeruginosa* isolates, respectively. These results showed that our CZA and C/T susceptibility rates were higher than these two studies. Probably, patterns of antibiotic usage resistance mechanisms and susceptibility rates to different antibiotics may differ by geographical region in the world, as well as Turkey, and could have affected the results.

Ceftolozane is a new oxyimino-aminothiazolyl cephalosporin with a structure similar to ceftazidime, but it is less susceptible to hydrolysis by AmpC and less affected by porin loss than ceftazidime^[8]. In our study, two isolates were resistant to CZA but susceptible to C/T and one isolate was resistant to both CZA and C/T. All isolates that were resistant to either ceftazidime-avibactam or ceftolozane-tazobactam were also resistant to all three beta-lactam agents. Although the number of isolates is low; according to these results, we can say that in our study C/T is more effective than CZA in ceftazidime resistant *P. aeruginosa* isolates. This finding is consistent with the findings by Buehrle et al.^[25].

This study has a few limitations. Firstly, the low number of tested isolates and the inclusion of a single hospital limit the statistical power of these results. Secondly, the mechanisms of resistance to CZA and C/T were not explored in this study. Unfortunately, there were no studies about the resistance mechanisms for CZA and C/T among *P. aeruginosa* isolates in Turkey.

In summary, in vitro studies have shown that CZA and C/T might be a good selection for the treatment of MDR/XDR *P. aeruginosa* infections, but clinical experience is currently limited. We hope that new studies about determination of resistance mechanisms may be helpful for development of effective strategies to cope with resistance and epidemiological purposes.

ETHICS COMMITTEE APPROVAL

The ethical approval for this study was obtained from Samsun Training and Research Hospital (Protocol No: SBÜSEAH-KAEH-2020/2/5).

CONFLICT of INTEREST

None of the authors had conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: MB, EB, Hİ

Data Collection or Processing: MB, EB

Analysis/Interpretation: MB, Hİ

Literature Search: MB, EB, Hİ

Writing: MB

Final Approval: MB, EB, Hİ

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