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COMPARISON OF IN VITRO ACTIVITY OF CEFDITOREN WITH OTHER ORAL ANTIBIOTICS AGAINST NOSOCOMIAL URINARY ESCHERICHIA COLI STRAINS

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ABSTRACT:

Purpose: Increasing resistance rates to oral antibiotics among nosocomial urinary *Escherichia coli* isolates limit the therapeutic options in the sequential therapy of nosocomial urinary tract infections. In this study, the in vitro activities of cefditoren and various oral antibiotics that could be candidates for the sequential therapy of nosocomial UTI were evaluated.

Materials and methods: Totally 99 *E. coli* isolates were studied. Antimicrobial susceptibilities of the strains were tested by agar dilution method for cefditoren, and by disk diffusion method for the other oral antibiotics. The double disk synergy method was used for detection of ESBL activity.

Results: Cefditoren MIC50 and MIC90 values were 1 mg/L and 128 mg/L, respectively, and 50% of the isolates were susceptible to cefditoren. The resistance rate was higher among ciprofloxacin resistant strains. In vitro activity of cefditoren was comparable to that of cefixime, and better than that of the other oral antibiotics, namely ciprofloxacin, TMP-SMZ, cefuroxime, and amoxicillin-clavulanate.

Conclusion: Cefditoren may be a candidate in the sequential therapy of nosocomial urinary tract infections. These observations need to be supported by clinical studies.

Key words: Cefditoren, Nosocomial, Urinary, *Escherichia Coli*.

NOZOKOMİYAL ÜRİNER ESCHERICHIA COLI İZOLATLARINDA SEFDİTORENİN IN VITRO ETKİNLİĞİNİN DİĞER ORAL ANTİBİOTİKLERLE KARŞILAŞTIRILMASI

ÖZ:

Amaç: Nozokomiyal üriner *E. coli* izolatları arasında oral antibiyotiklere karşı yüksek direnç oranları bu infeksiyonların ardışık tedavisindeki seçenekleri kısıtlamaktadır. Bu çalışmada, nozokomiyal üriner sistem infeksiyonlarının ardışık tedavisinde kullanılabilecek çeşitli oral antibiyotikler ve sefditorenin in vitro aktiviteleri değerlendirilmiştir.

Materyal ve metod: Çalışmada toplam 99 *E. coli* suşu yer almıştır. Suşların antimikrobiyal duyarlılıkları sefditoren için agar dilüsyon metoduyla, diğer oral antibiyotikler için ise disk difüzyon metoduyla belirlenmiştir. ESBL aktivitesinin saptanması için çift disk sinerji metodu kullanılmıştır.

Bulgular: Sefditorenin MİK50 ve MİK90 değerleri sırasıyla 1 mg/L ve 128 mg/L olarak saptanmıştır. Çalışmaya alınan izolatların %50'si sefditorene duyarlı olarak kabul edilmiştir. Siprofloksasine dirençli olan suşlar arasında direnç oranları daha yüksek bulunmuştur. Sefditorenin in vitro etkinliği sefiksime benzer, diğer oral antibiyotikler olan siprofloksasin, trimetoprim-sulfametoksazol, sefuroko/sim ve amoksisilin-klavulanattan daha iyi olarak saptanmıştır.

Sonuç: Çalışmamızın sonuçlarına göre sefditoren nozokomiyal üriner sistem infeksiyonlarının ardışık tedavisi için bir seçenek olabilir. Ancak bu gözlemlerin klinik çalışmalarla desteklenmesi gereklidir.

Anahtar kelimeler: Sefditoren, Nozokomiyal, Üriner, *Escherichia Coli*

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INTRODUCTION

Nosocomial urinary tract infections (UTIs) are the most frequently encountered nosocomial infections in hospital settings. They are responsible for 40% of nosocomial infections.[1] *Escherichia coli* is the most common urinary pathogen isolated from UTIs.[1,2] High resistance rates against oral antimicrobial agents among nosocomial *E. coli* isolates limit the therapeutic options in sequential therapy. The duration of hospitalization of the patients is lengthened because of the requirement for parenteral antibiotic treatment, and the cost is increased.

The most frequently used oral antibiotics in the treatment of UTIs are trimethoprim-sulfamethoxazole (TMP-SMZ), quinolones, amoxicillin-clavulanate, and second and third generation cephalosporins. Cefixime, a third generation oral cephalosporin, is more effective than the other oral cephalosporins against urinary pathogens, and is used for the treatment of complicated UTIs.[3] Cefditoren, a new third generation oral cephalosporin recently introduced into clinical usage in Turkey, is effective primarily against respiratory pathogens, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. It is also active against methicillin sensitive *Staphylococcus aureus* and members of Enterobactericeae.[4,5] Cefditoren is mainly excreted via the renal system, but there are no data about its use in the treatment of UTIs.

In this study, the in vitro activities of cefditoren and various oral antibiotics that could be candidates for the sequential therapy of nosocomial UTIs were evaluated.

MATERIALS AND METHODS

Ninety-nine *E. coli* strains isolated from nosocomial UTIs were included in the study. The strains were obtained from urinary samples of patients from various clinics between January and April 2005. The diagnosis of nosocomial UTI was made according to Center for Diseases Control and Prevention criteria.[6] The BBL Crystal Enteric/Nonfermenter ID Kit (Becton Dickinson, USA) was used for the identification of strains.

Cefditoren minimum inhibitory concentration (MIC) values were detected by the agar dilution method. The values ≤1 mg/L indicated susceptibility.[7] Antimicrobial susceptibilities of the other oral antibiotics, ciprofloxacin, amoxicillin-clavulanate, TMP-SMZ, cefuroxime, and cefixime, were tested by disk diffusion method according to the CLSI criteria.[8] The double disk synergy method was used for detection of extended spectrum beta-lactamase (ESBL) activity.[9] For testing, the test inoculum (0.5 McFarland turbidity) was spread

onto Mueller-Hinton agar (MHA; HiMedia, India) using a sterile cotton swab. Then ceftriaxone, cefotaxime, cefepime, and ceftazidime disks were placed at a distance of 20 mm from the amoxicillin-clavulanate disk on the surface of MHA. The plate was incubated at 37 °C overnight. The organisms were considered to be producing ESBL when the zone of inhibition around any of the expanded-spectrum cephalosporin disks showed a clear-cut increase towards the amoxicillin-clavulanate disk. *E. coli* ATCC 25922 and *Klebsiella pneumoniae* ATCC 700603 were used as negative and positive control reference strains, respectively.

RESULTS

Cefditoren MIC50 and MIC90 values were 1 mg/L and 128 mg/L, respectively (MIC range from 0.12 to 128 mg/L), and 50.5% (50/99) of the isolates were found to be susceptible to cefditoren in our study. Antimicrobial susceptibilities of the other oral antibiotics are shown in Table 1.

Table 1. Antimicrobial susceptibilities of nosocomial urinary *E. coli* isolates to various oral antibiotics.

Antibiotic	Susceptible(%)	Intermediate (%)	Resistant(%)
Amoxiycillin/clavulanate	45	36	19
Cefuroxime	26	25	49
Cefixime	51	1	48
Ciprofloxacin	23	1	76
TMP-SMZ*	32	-	68

*Trimethoprim-sulfamethoxazole

ESBL activity was detected in 58.5% (58/99) of the isolates. All isolates resistant to cefixime and cefditoren had ESBL activity. Additionally, 10 isolates susceptible to cefixime and 8 isolates susceptible to cefditoren showed ESBL activity.

In the present study, 76% of the *E. coli* strains were resistant to ciprofloxacin. The resistance rates for the other oral antibiotics were higher among ciprofloxacin-resistant strains (Table 2). Cefditoren MIC_{50} and MIC_{90} values were 0.5 mg/L and 32 mg/L among the ciprofloxacin-susceptible strains, and 128 mg/L and 128 mg/L among ciprofloxacin-resistant strains. ESBL activity was positive in 69.7% and 17.4% of ciprofloxacin-resistant and susceptible strains, respectively.

Table 2. Resistance rates to the other oral antibiotics among ciprofloxacin-resistant and susceptible isolates (%).

Antibiotic	CIP-S (n:23)	CIP-R (n:76)
Amoxiycillin/clavulanate	26	63.2
Cefuroxime	13	59.2
Cefixime	13	57.9
TMP-SMZ	39.1	76.3
Cefditoren	13	57.9

CIP-S: Ciprofloxacin-susceptible,
CIP-R: Ciprofloxacin-resistant,
TMP-SMZ: Trimethoprim-sulfamethoxazole

DISCUSSION

The frequency of *E. coli* in nosocomial UTIs is lower than in community acquired UTIs. However, nosocomial UTIs mostly develop due to resistant strains[1,2]. The high resistance rates to oral antimicrobial agents limit the therapeutic options in sequential therapy, and lead to lengthening of the duration of hospitalization.

Sucu et al. have reported the resistance rates of uropathogenic *E. coli* strains to various antibiotics evaluated in several studies conducted in this country. Of the nosocomial urinary *E. coli* strains, 40%-61% were resistant to TMP-SMZ and 7.3%-75% to cefuroxime.[10] In the last decade, their use in the empirical treatment of UTIs, even in community acquired infections, has been limited due to high resistance rates. Quinolones have become the most commonly used antibiotics in empirical treatment. However, the increasing resistance rate among urinary pathogens is worrisome. Quinolone resistance was reported to be 2%-20% in community acquired *E. coli* isolates, and 36% in nosocomial isolates.[1,11] In our study, antimicrobial susceptibilities of *E. coli* isolates to various oral antibiotics were as follows: 45% for amoxicillin-clavulanate, 26% for cefuroxime, 51% for cefixime, 23% for ciprofloxacin, and 32% for TMP-SMZ. Especially high resistance rates of ciprofloxacin among *E. coli* strains were considered to be associated with excessive and inappropriate use of quinolones in our hospital.

The difference in resistance to oral antimicrobial agents between ciprofloxacin resistant and susceptible strains was noteworthy. In the ECO-SENS Project, cross and associated resistance was investigated in *E. coli* isolated from noncomplicated UTIs. Resistance to any antimicrobial agent was found to be associated with increased resistance to the other antimicrobial agents, except fosfomycin. For example, gentamicin resistance was 28.6% in ciprofloxacin-resistant *E. coli*

isolates and 0.3% in susceptible strains.[12] It is concluded that ciprofloxacin resistance is progressively widening in European countries, and a multidrug resistant phenotype is not only related to use of quinolones, but also to ampicillin/amoxicillin, and TMP-SMZ. In another study, increased MIC levels for ciprofloxacin among urinary *E. coli* isolates were found to be associated with increased ampicillin, TMP-SMZ, nitrofurantoin, and cefdinir resistance. Approximately 90% of isolates resistant to ciprofloxacin were also resistant to at least one or two additional agents, most commonly ampicillin and TMP-SMZ.[13] Ciprofloxacin use, age over 50, and complicated UTIs were reported to be independent risk factors contributing to ciprofloxacin resistance.[14]

Cefditoren, an oral third generation cephalosporin recently introduced into clinical use in this country, is effective against respiratory pathogens. Its in vitro activity against members of Enterobactericeae, especially to *E. coli*, has been demonstrated.[4,5] In our study, the highest susceptibility rates for *E. coli* were detected to cefixime and cefditoren. In vitro activity of cefditoren was comparable to that of cefixime, and better than that of the other oral antibiotics: ciprofloxacin, TMP-SMZ, cefuroxime, and amoxicillin-clavulanate. Although the resistance rate for cefditoren was higher in ciprofloxacin-resistant strains, 40% of them were still susceptible to cefditoren. Cefditoren was not effective against ESBL producing strains, and these strains should be reported as resistant to cefditoren even though in vitro test results showed susceptibility. Routine susceptibility test results for cefditoren should be interpreted as the other oral and parenteral third generation cephalosporins. Cefditoren is licensed for the treatment of upper and lower respiratory tract infections and skin-soft tissue infections in this country. Cefditoren is excreted mostly from the kidneys, and so it may be a candidate for the sequential therapy of UTIs. However, these observations need to be supported with clinical studies.

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