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Investigation of *In Vitro* Activity of Mecillinam Against Isolates of Enterobacteriaceae

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Abstract

Introduction: Mecillinam is an oral antibiotic with excellent clinical efficacy in the treatment of uncomplicated UTIs. It is a betalactam antibiotic and active against Enterobactericeae but has little activity against Gram positive bacteria. In this study, we aimed to investigate the in vitro activity of mecillinam against Enterobactericeae isolates that were isolated from different clinical specimens.

Materials and methods: Identification of the bacterial isolates were tested by conventional methods and Phoenix (Becton Dickinson, USA) and Vitek MS (Biomeriux, France) automated systems. Antimicrobial susceptibility was performed by using the disk diffusion method and Phoenix (Becton Dickinson, USA) and Vitek2 Compakt (Biomeriux, France) autometed systems. Mecillinam susceptibility of the isolates were determined by disc diffusion method by using 10 µg mecillianm disc and interpreted according to the EUCAST criteria.

Results: Total of 338 Enterobactericeae (*E. coli* n=162, *Klebsiella* spp. n=142, *Enterobacter* spp. n=18, *Proteus* spp. n=10, *Citrobacter* spp. n=4, *Salmonella* spp. n=2) isolates were tested. Most of the clinical specimens were urinary specimens (n=272, 80.5%). Mecillinam susceptibility was detected as 82.5%. Mecillinam susceptibility for urinary tract isolates was 87.1%. In this study, 57% of imipenem resistant isolates were determined susceptible for mecillinam.

Conclusion: In conclusion, Mecillinam could be a good option, especially for urinary tract infections.

Keywords: Mecillinam; Enterobactericeae; Susceptibility

1. Introduction

Mecillinam is an antibiotic from beta-lactam group. Contrary to penicillin and cephalosporins, instead of 6-amidino, its structure contains 6-acylamino side chains. It is effective against Gram negative bacteria, particularly from Enterobactericeae family, while its effect against Gram positive bacteria is low [1]. Upon examining the efficiency of mecillinam, it was observed that no enzyme participating in the synthesis of cell wall was inhibited and that spheroplasts with rapid lysis were not formed. It is considered that the efficiency of mecillinam comes from its affinity to penicillin-binding protein 2. Contrary to the majority of other beta-lactam antibiotics, it does not bind with penicillin-binding protein 1 or 3 [2,3]. Also, due to its resistance to the effect of beta-lactamase hydrolysis, it has more effect on Enterobactericeae [4]. When taken orally, 21% of the mecillinam dose is disposed of urinary (three inactive metabolites and one active metabolite), while an important amount is released through the biliary tract.

Mecillinam, especially in North European countries, is a preferred choice in the treatment of non-complicated infections of lower urinary tract because of its high-tolerability and low side effects profile [5]. Mecillinam is not the preferred and frequently used antibacterial agent in our country. However, because of the rapidly increasing resistance today, we believe that in the following years it may become a good choice for treating non-complicated infections of lower urinary tract.

Susceptibility of gram negative bacteria to mecillinam has not been studied in our country. In this study, our goal is not just to examine urinary system parameters, but also to examine in vitro effectiveness of mecillinam on gram negative bacteria isolated from other clinical examples, thus providing a contribution to the literature.

2. Material and Methods

In the study, 338 Enterobactericeae isolated from clinical samples was tested. The identification of bacteria was conducted using conventional methods (EMB Agar colony view, oxidase reaction, TSI, Indole), and urea, motion and citrate reproduction properties using Pheonix (Becton Dickinson, USA) and Vitek MS (Biomeriux, France) automatized systems. Antimicrobial susceptibility of bacterial isolates was examined with disk diffusion method using Pheoenix (Becton Dickinson, USA) and Vitek2 Compakt (Biomeriux, France) automatized system. Susceptibility to mecillinam was examined using 10 µg mecillinam disk and MHA medium with KirbyBauer disk diffusion method. The results were evaluated according to susceptibility limit values (≥15 susceptible, 15> resistant) proposed for *E. coli*, *Klebsiella* spp. and *Proteus mirabilis* isolated from EUCAST urinary system samples [6].

3. Results

Total of 162 *E. coli*, 142 *Klebsiella* spp., 18 *Enterobacter* spp., 10 *Proteus* spp., 4 *Citrobacter* spp., 2 *Salmonella* spp. isolates were tested in the study.

A significant part of sample types in the study consists of urinary isolates (n=272, 80.5%). Besides that, blood (n=23, 6.8%), contusion (n=24, 7.1%), respiratory tract (n=9, 2.6%), stools (n=2, 0.6%) and sterile body fluid (n=1, 0.3%) samples were also included in the study. Susceptibility to mecillinam was determined to be 82.5%. When the susceptibility to mecillinam was examined according to sample types, the susceptibility to mecillinam in urine isolates was 87.1%. Susceptibility to mecillinam according to sample types is given in Table 1.

Specimen (n)	Susceptibility to mecillinam
Urine (272)	237 (87.1%)
Contusion (24)	13 (54.1%)
Blood (23)	19 (82.6%)
Respiratory tract (9)	7 (77.7%)
Sterile body fluid (1)	1 (100%)
Stools (2)	2 (100%)

Table 1: Susceptibility of mecillinam according to specimens.

The most tested isolate in the study was *E. coli* (n=162), followed by *Klebsiella* spp. (n=142) isolates. Susceptibility to mecillinam in *E. coli* isolates was 94%. In *Citrobacter* spp. (n=4) and *Salmonella* (n=2) isolates, susceptibility was 100%, however the number of tested isolates was very small (Table 2).

Bacteria (n)	Susceptibility to mecillinam n(%)
E. coli (162)	152 (94%)
Klebsiella spp. (142)	98 (69%)
Enterobacter spp. (18)	16 (89%)
Proteus spp. (10)	7 (70%)
Citrobacter spp.(4)	4 (100%)
Salmonella spp.(2)	2 (100%)

Table 2: Susceptibility of mecillinam according to bacterial isolates

The susceptibility to mecillinam of isolates resistant to amoxicillin-clavulanic acid, nitrofurantoin, trimethoprim-sulfamethoxazole and ciprofloxacin which are often used for treatment of urinary tract infections was 75%, 67%, 76% and 78% respectively. Distribution according to bacteria types is given in Table 3. 61 imipenem-resistant isolate's susceptibility to mecillinam was 57% (n=35) in our study (Table 4).

	AMC(R)/MES (S)	NF (R)/MES (S)	SXT (R)/MES (S)	CİP (R)/MES (S)
Citrobacter spp.	2/2	-	-	-
E. coli	31/29	4/3	47/42	45/43
Enterobacter spp.	9/8	4/4	1/1	
Klebsiella spp.	59/37	40/24	44/27	69/35
Proteus spp.	1/1	4/4	2/2	1/1
	102/77(75%)	52/35(67%)	94/72(76%)	86/67(78%)

Table 3: Susceptibility of mecillinam in urine isolates resistant to amoxicillin-clavulanic acid, nitrofurantoin and trimethoprim-sulfamethoxazole

Bacteria	IMI (R)/MES (S)
E. coli	20/18
Klebsiella	41/17

Table 4: Susceptibility of mecillinam in imipenem-resistant isolates

4. Discussion

Fosfomycin trometamol, mecillinam and nitrofurantoin are recommended the first for the treatment of non-complicated urinary tract infections. Also, if the resistance rate to trimethoprim is not over 20%, trimethoprim-sulfamethoxazole can be recommended for the first stage of the treatment as well [7]. The bacteria most frequently isolated from infections of urinary tract is *E. coli* (80%). In the conducted studies it has been determined that *E. coli* is highly resistant to ampicillin, sulfamethoxazole, trimethoprim and trimethoprim-sulfamethoxazole antibiotics. Even though mecillinam is not preferred in our country, it is the preferred agent for treating infections of urinary tract around the world, especially in North European countries. For this reason, it is advised to use mecillinam,

nitrofurantoin and phosphomycin for the treatment of infections of urinary tract caused by *E. coli* [8]. In the study by Wootton et al, the resistance to mecillinam of *E. coli* isolates was determined to be 6.5% [9]. It was determined that the resistance to mecillinam of *E. coli* isolates obtained from community-onset urinary tract infections from five European countries (Austria, Portugal, Greece, United Kingdom and Sweden) was between 0-1,4%. The highest resistance rates with 1.4% were determined in Greece and Portugal [8]. In our study, the resistance of *E. coli* isolates to mecillinam was determined to be 6%. This resistance rate is rather low, even if it is slightly higher than the resistance rates in other European countries.

In a study conducted in Canada, 2000 urinary tract isolates' susceptibility to ampicillin, trimethoprim-sulfamethoxazole, mecillinam, nitrofurantoin and ciprofloxacin was examined and the resistance rates were 41.1%, 19.2%, 14.7%, 5.0% and 1.8% respectively. In the same study, it was determined that a significant portion of *E. coli* isolates resistant to ampicillin, trimethoprim-sulfamethoxazole or ciprofloxacin were susceptible to mecillinam [10]. In our study, the susceptibility to mecillinam of isolates resistant to amoxicillin-clavulanic acid, nitrofurantoin, trimethoprim-sulfamethoxazole and ciprofloxacin was 75%, 67%, 76% and 78% respectively.

In the study by Mazzuli et al. [4] susceptibility to mecillinam was examined on gram negative bacteria isolated from urinary tract infections and the susceptibility of *E. coli, Klebsiella* spp., *Enterobacter* spp., *Proteus* spp, and *P. aeruginosa* was 99.7%, 100%, 100%, 97.6% and 57.1% respectively. It was determined in the same study that the activity of mecillinam is stronger than the activity of ampillicin, trimethoprim-sulfamethoxazole and nitrofurantion, but weaker than the activity of ciprofloxacin [4].

When compared to other groups of beta-lactam antimicrobials, it was observed that mecillinam exhibited more effectiveness and stability than beta-lactamase producing isolates such as TEM, IRT and AmpC [11]. There are studies that demonstrate the effectiveness of mecillinam against isolates with various resistance determinants [1,12,13]. In a study conducted in India on the subject of extended spectrum beta-lactamase positive (GSBL) *E. coli* isolates' susceptibility to mecillinam, mecillinam resistance rate was 4.5% [12]. Also, mecillinam exhibited low minimum inhibitory concentration values in GSBL positive isolates and its efficiency increased further with beta-lactamase inhibitory combinations [1]. Since mecillinam resistance rate of NDM-1 positive *E. coli* isolates was determined to be as low as around 3,5%, it is believed that mecillinam can be a good choice for treatment of infections caused by this bacteria [13]. As for our study, it was observed that 57% of carbapenem-resistant isolates were susceptible to mecillinam.

Mecillinam in vitro efficiency was examined in this study on sample types other than urine samples, but on a limited scale. High mecillinam susceptibility rates were observed, except in urine isolates, especially in bacterias isolated from blood culture. Even though mecillinam has been widely used in Scandinavian countries for a long time now, resistance increase has not been observed and despite its use as only medicine for treatment of urinary tract infections, it did not cause resistance increase [14]. It should be remarked that in our study over 90% susceptibility rate was determined for *E. coli* isolates, one of the most frequent causes for urinary tract infections. We believe that,

as the number of related studies increase and mecillinam enters clinical use, the effect of this antibiotic on the isolates in our country will be understood better.

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