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Treatment efficacy and superinfection rates in complicated urinary tract infections treated with ertapenem or piperacillin tazobactam

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Background/aim: In this retrospective study, the efficacy of ertapenem and piperacillin tazobactam was compared in the treatment of complicated urinary tract infections (cUTIs). Treatment responses were also evaluated for both antibiotics.

Materials and methods: A total of 230 patients were enrolled in the study. Of these, 170 received ertapenem and 60 received piperacillin-tazobactam.

Results: In both groups, urine cultures after 48 h were negative for the initial uropathogen. The frequency of superinfection was 29.4% in the ertapenem group and 8.3% in the piperacillin-tazobactam group over the duration of treatment ($P < 0.05$). Urinary catheterization increased the superinfection risk 2.88-fold in the ertapenem group and diabetes mellitus increased the risk 8.50-fold in the piperacillin-tazobactam group (CI: 1.44–5.76 and 1.16–62.09, respectively, $P < 0.05$). The main pathogen isolated from superinfection in the ertapenem group after 48 h was Enterococcus spp. (71.4%).

Conclusion: Both ertapenem and piperacillin-tazobactam were effective in the treatment of cUTIs caused by ESBL-producing microorganisms. A high frequency of superinfection in the ertapenem group was the result of Enterococcus and Pseudomonas spp., against which ertapenem is not active. In the presence of urinary catheterization, diabetes mellitus, and urological intervention, patients should be closely monitored for the development of a superinfection, especially patients receiving ertapenem.

Key words: Complicated urinary tract infection, ertapenem, piperacillin-tazobactam, efficacy, superinfection

1. Introduction

Complicated urinary tract infections (cUTIs) are a major cause of hospital admissions and are the most frequent cause of nosocomial infections. They are also associated with significant morbidity and increased healthcare costs (1). Resistance to first-line antimicrobials, such as fluoroquinolones, cotrimoxazole, and oral cephalosporins, among urinary *Escherichia coli* and *Klebsiella* isolates limits the therapeutic options in some geographic regions, including Turkey. Carbapenems and betalactam/betalactamase inhibitor combinations remain the drugs of choice for the treatment of severe infections due to extended spectrum beta-lactamase (ESBL)producing Enterobacteriaceae (1,2). Few studies have evaluated the comparative activity of carbapenems and beta-lactam/beta-lactamase inhibitor combinations.

In this study, we aimed to compare the activity of ertapenem and piperacillintazobactam for the treatment of cUTIs due to ESBL-producing *E. coli* and *Klebsiella* spp. We also analyzed the risk factors for the development of a superinfection during treatment.

2. Materials and methods

This study was conducted retrospectively with patients who had been hospitalized in various clinics of Gazi University Hospital from January 2008 to April 2012. During this period, patients were included if they were diagnosed as having a cUTI due to ESBLproducing *E. coli* and *Klebsiella* spp. The patients were separated into two groups according to whether they received ertapenem or piperacillin-tazobactam treatment.

The patients' data were obtained from their files and laboratory records. Data from patients who grew $\geq 10^5$ colony forming units (cfu) of ESBL-positive *E. coli* and *Klebsiella* spp. in baseline urine cultures and were treated for cUTIs were analyzed retrospectively for cUTI risk factors. The presence of functional and anatomical defects, an indwelling catheter, immunosuppression, recurrent

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urinary tract infections, prior antibiotic use, diabetes mellitus, urological interventions, and nephrolithiasis were accepted as markers of a cUTI (3). Patients less than 18 years of age and patients who were treated with antibiotics other than ertapenem and piperacillin-tazobactam were excluded from the study.

The microbiological response of each patient was evaluated after 48 h of treatment, and then once again (median: 5th day) during the treatment. Microbiological responses were defined as follows: eradication (uropathogen $\geq 10^5$ cfu/mL at entry reduced to $<10^4$ cfu/mL); persistence (urine culture grew $\geq 10^4$ cfu/mL of an initial uropathogen); and superinfection (urine culture during therapy grew $\geq 10^5$ cfu/mL of a pathogen other than the initial pathogen) (4). Treatment responses (eradication, persistence, and superinfection), outcomes, and the risk factors for cUTI in both the ertapenem and piperacillin-tazobactam groups were compared using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). The risk factors affecting the development of a superinfection were also analyzed. Continuous variables are presented as mean ± standard deviation and median (minimum, maximum), while categorical variables are given as a number and percentage. Continuous variables were compared with the Mann–Whitney U test and categorical variables with the chisquare test. $P < 0.05$ was considered significant.

Logistic regression (LR) models were built to determine the risk factors of a superinfection (last step was presented, method: backward LR, entry: 0.05, removal: 0.10). The LR model of superinfections under treatment included urinary catheterizations, nephrolithiasis, diabetes mellitus, urological interventions, immunosuppression, recurrent urinary tract infections, and antibiotic treatment within the last 3 months. The LR model for the risk factors of an enterococcal superinfection in the ertapenem group included urinary catheterizations, nephrolithiasis, diabetes mellitus, urological interventions, urinary malignancies, recurrent urinary tract infections, and antibiotic treatment within the last 3 months.

3. Results

A total of 230 patients were enrolled in this study. Of these, 170 received ertapenem and 60 received piperacillin-tazobactam. The distribution of the patients' descriptive characteristics is presented in Table 1. The frequency of malignancy, history of recurrent urinary tract infections,

Table 1. Distribution of patients' descriptive characteristics.

Characteristics		Ertapenem (n = 170) (n, %)	Piperacillin-tazobactam (n = 60) (n, %)	P
Age, mean ± SD, median (min, max)		59.54 ± 16.80, 61.0 (18, 95)	57.63 ± 18.62, 60.50 (18, 90)	0.95
Sex	Female	79 (46.47)	28 (46.66)	0.79
	Male	91 (53.53)	32 (53.34)	
Duration of treatment, mean ± SD, median (min, max)		10.89 ± 5.22, 10 (2, 34)	10.25 ± 4.77, 10 (2, 32)	0.05
Diabetes mellitus		44 (25.9)	12 (20.0)	0.46
Malignancy		38 (22.4)	5 (8.3)	0.02
Urinary tract malignancy		26 (15.3)	12 (20.0)	0.52
Immunosuppression		25 (14.7)	15 (25.0)	0.10
Recurrent urinary tract infection		47 (27.6)	32 (53.3)	0.001
Nephrolithiasis		26 (15.3)	15 (25.0)	0.13
Neurogenic bladder		20 (11.8)	9 (15.0)	0.67
Urinary incontinence		7 (4.1)	2 (3.3)	1.00
Urethral stricture		15 (8.8)	4 (6.7)	0.78
Hyperplasia of prostate		36 (21.2)	8 (13.3)	0.25
Urinary catheterization		72 (42.6)	37 (61.7)	0.17
Antibiotic treatment within last 3 months		53 (31.2)	32 (53.3)	0.02
Urological intervention		60 (35.3)	29 (48.3)	0.07

and the presence of antibiotic treatment within the last 3 months were significantly different between the ertapenem and piperacillintazobactam treatment groups (P < 0.05).

In both groups, urine cultures after 48 h were negative for the initial uropathogens. However, the frequency of superinfections was 29.4% in the ertapenem group and 8.3% in the piperacillin-tazobactam group over the duration of the treatment. This difference between groups was statistically significant (P < 0.05). The frequency of superinfection in both groups is shown in Table 2.

Thirty-five patients developed a superinfection in the ertapenem group; at the 48-h urine culture, the isolated microorganisms included *Enterococcus* spp. (n = 25), *Pseudomonas* spp. (n = 4), *Candida* spp. (n = 4), and *S. maltophilia* (n = 2). In the piperacillin-tazobactam group, only five patients had superinfections and all of these were due to *Candida* spp.

Urine cultures after the 48th hour of treatment were positive in 22 patients in the ertapenem group and in one patient in the piperacillin-tazobactam group. The isolated microorganisms included *Enterococcus* spp. (n = 13), *Candida* spp. (n = 6), *S. maltophilia* (n = 2), and *Pseudomonas* sp. (n = 1) in the ertapenem group and *Candida* sp. (n = 1) in the piperacillin-tazobactam group. Of seven patients in the ertapenem group and one patient in the piperacillin-tazobactam group, urine cultures grew different microorganism at the 48th and after the 48th hour.

Superinfection risk factors for the total duration of treatment were analyzed using the LR model. Urinary catheterization increased the superinfection risk 2.88-fold (CI: 1.44–5.76) in the ertapenem group (P < 0.05), and diabetes mellitus increased the risk 8.50-fold (CI: 1.16–62.09) fold in the piperacillin-tazobactam group (P < 0.05).

The main pathogen isolated from superinfections in the ertapenem group after 48 h was *Enterococcus* spp. (71.4%). When the risk factors for an enterococcal superinfection were analyzed, it was found that urinary catheterization and urological intervention were significant risk factors (Table 3).

In 43 (78.1%) of the 55 patients that developed a superinfection, the initial therapy was changed, or a new antibiotic (teicoplanin, fluconazole, etc.) was added to the therapy. The duration of the treatment was significantly longer in patients with superinfections (14 ± 6.6 days vs. 10 ± 4.2 days, P < 0.001).

4. Discussion

ESBL production has become more common among *E. coli* and *Klebsiella* spp. isolated from urinary tract infections worldwide. Among these isolates, resistance to other classes of antibiotics, such as fluoroquinolones and aminoglycosides, limits the therapeutic options in UTIs. Carbapenems and beta-lactam/beta-lactamase inhibitor combinations are used frequently in the treatment of UTIs

Table 2. The frequency of superinfection under treatment.

Superinfection	Ertapenem (n = 170) (n, %)	Piperacillin-tazobactam (n = 60) (n, %)	P
48th hour of treatment	35 (20.6)	5 (8.3)	0.05
After 48th hour of treatment	22 (12.9)	1 (1.7)	0.02
Total	50 (29.4)	5 (8.3)	0.02

Table 3. Risk factors for the enterococcal superinfection in ertapenem group at 48th hour of treatment.

	P	OR	CI
Catheterization	0.048	2.54	1.01–6.42
Diabetes mellitus	0.048	2.59	1.01–6.66
Urological intervention	0.018	2.99	1.20–7.43

The logistic regression model for the risk factors of enterococcal superinfection in ertapenem group at 48th hour of treatment includes urinary catheterization, nephrolithiasis, diabetes mellitus, urological intervention, urinary malignancy, recurrent urinary tract infection, and antibiotic treatment within last 3 months. OR: Odds ratio, CI: confidence interval.

caused by ESBL-producing enteric bacteria. Hsueh et al. stated that ESBL production among *E. coli* isolates in the Asia-Pacific region reached 33%, and nearly half of the isolates were also resistant to quinolones (2). In this study, carbapenems, including ertapenem, were suggested in the empirical therapy of cUTIs because there is no resistance to these agents. In a Spanish study, ertapenem was very active in vitro against urinary isolates of ESBLproducing Enterobacteriaceae (5). All of the isolates were susceptible to ertapenem. However, the susceptibility rates to other antimicrobials were low, for instance 15.5% to quinolones, 37.9% to cotrimoxazole, and 77.1% to piperacillin-tazobactam.

One of the important findings of our study was that both ertapenem and piperacillin-tazobactam were very effective in the treatment of cUTIs caused by ESBLpositive *E. coli* and *Klebsiella* spp. Urine cultures obtained at the 48th hour of treatment were negative for the primary pathogen in both treatment groups. Ertapenem, a group 1 carbapenem, seems to be a very good option in the treatment of cUTIs because of its activity against ESBL-positive microorganisms, its elimination by the renal route, and its pharmacokinetic properties, which allow its use as a once-per-day treatment (6). In the literature, the efficacy of ertapenem in UTI treatments was mostly compared to ceftriaxone. In a prospective, randomized, double-blind, multicenter study, Tomera et al. reported similar microbiological success rates for the ertapenem and ceftriaxone groups (91.8% vs. 93.0%, respectively) (7). In a more recent randomized, double-blind, multicenter study, the efficacies of ertapenem and ceftriaxone were compared in acute pyelonephritis and other cUTIs. A favorable microbiological response was observed in 87.0% and 88.7% of the patients in the ertapenem and ceftriaxone groups, respectively (4).

Piperacillin-tazobactam, a beta-lactam/beta-lactamase inhibitor, is also effective in the treatment of various infections caused by ESBL-positive microorganisms. It is widely used in the treatment of UTIs, lower respiratory tract infections, bloodstream infections, intraabdominal infections, and complicated skin and soft tissue infections (8). Sifuentes-Osornio et al. suggested that piperacillin-tazobactam is a reliable therapy in the treatment of cUTIs requiring hospitalization (9). They reported seeing favorable clinical responses with piperacillin-tazobactam in 83.6% and 80.0% of early and late assessments, respectively. Piperacillin-tazobactam was as effective as imipenem-cilastatin for the treatment of acute complicated pyelonephritis and cUTIs, with 83.0% and 79.9% clinical success, respectively (10). There were no studies comparing the efficacy of ertapenem and piperacillin-tazobactam in the treatment of cUTIs due to ESBL-producing *E. coli* and *Klebsiella* spp. until the current study. Therefore, our study provides valuable data concerning the use of ertapenem and piperacillin-tazobactam for these infections. When we compared ertapenem and piperacillin-tazobactam, both were effective in the treatment of cUTIs, and there was no statistical difference between their activities. However, it seems that ertapenem has some advantages because of both its onceper-day usage and its convenience as an outpatient parenteral antibiotic therapy (11).

According to our results, the most important finding was the difference in frequency of superinfections between the groups. The frequency of a superinfection was significantly higher in the ertapenem group. We detected a superinfection in one-third of patients in the ertapenem group; however, this rate was only one-tenth in the piperacillintazobactam group. The difference between the two groups was the result of *Enterococcus* and *Pseudomonas* spp., against which ertapenem is not active (11). The LR model revealed that urinary catheterization was an independent risk factor for the development of a superinfection in the ertapenem group, and the presence of diabetes mellitus in the piperacillin-tazobactam group.

In the ertapenem group, *Enterococcus* spp. was the main pathogen isolated from superinfections and was detected in 71.4% of positive urine cultures after 48 h. Urinary catheterization, diabetes mellitus, and urological intervention were significant risk factors for the development of an enterococcal superinfection. Ertapenem has no activity against *Enterococcus* spp. or *Pseudomonas* spp. Therefore, we recommend that ertapenem should be cautiously used in cases where there is a suspicion of *Enterococcus* and *Pseudomonas*, especially in patients with urinary catheterization, diabetes mellitus, or urological intervention. Urine cultures should be performed at the 48th hour for the detection of a superinfection.

As a result of superinfection, duration of treatment lengthens; however, this did not cause mortality in our study.. The duration of treatment was significantly longer in patients who had developed a superinfection ($P < 0.01$).

In conclusion, both ertapenem and piperacillin-tazobactam were effective in the treatment of cUTIs caused by ESBL-producing enteric gram-negative bacteria. The frequency of superinfections in the ertapenem group was significantly higher than in the piperacillin-tazobactam group. In the presence of urinary catheterization, diabetes mellitus, and urological intervention, patient should be closely monitored for the development of a superinfection, especially patients receiving ertapenem.

References

1. Bader MS, Hawboldt J, Brooks A. Management of complicated urinary tract infections in the era of antimicrobial resistance. Postgrad Med 2010; 122: 7-15.
2. Hsueh PR, Hoban DJ, Carmeli Y, Chen SY, Desikan S, Alejandria M, Ko WC, Binh TQ. Consensus review of the epidemiology and appropriate antimicrobial therapy of complicated urinary tract infections in Asia-Pacific region. J Infect 2011; 63: 114-123.
3. Neal DE. Complicated urinary tract infections. Urol Clin N Am 2008; 35: 13-22.
4. Park DW, Peck KR, Chung MH, Lee JS, Park YS, Kim HY, Lee MS, Kim JY, Yeom JS, Kim MJ. Comparison of ertapenem and ceftriaxone therapy for acute pyelonephritis and other complicated urinary tract infections in Korean adults: a randomized, double-blind, multicenter trial. J Korean Med Sci, 2012; 27: 476-483.
5. Tamayo J, Orden B, Cacho J, Cuadros J, Gomes-Gorces JL, Alos JI. Activity of ertapenem and other antimicrobials against ESBL-producing enterobacteria isolated from urine in patients from Madrid. Rev Esp Quimioterap 2007; 20: 334-338.
6. Shah PM, Isaacs RD. Ertapenem, the first of a new group of carbapenems. J Antimicrob Chemother 2003; 52: 538-542.
7. Tomera KM, Burdmann EA, Reyna OGP, Jiang Q, Wimmer WM, Woods GL, Gesser RM; Protocol 014 Study Group. Ertapenem versus ceftriaxone followed by appropriate oral therapy for treatment of complicated urinary tract infections in adults: result of a prospective, randomized, double-blind, multicenter study. Antimicrob Agents Chemother 2002; 46: 2895-2900.
8. Gin A, Dilay L, Karlowsky JA, Walkty A, Rubinstein E, Zhanel GG. Piperacillin-tazobactam: a beta-lactam/beta-lactamase inhibitor combination. Expert Rev Anti Infect Ther 2007; 5: 365-383.
9. Sifuentes-Osornio J, Jakob E, Clara L, Durlach R, Dain A, Ruìz-Palacios GM, Barkan L, Lamberghini R, Jáuregui A, Villalobos Y et al. Piperacillin/tazobactam in the treatment of hospitalized patients with urinary tract infections: an open non-comparative and multi-centered trial. J Chemother 1996; 8: 122-129.
10. Naber KG, Savov O, Salmen HC. Piperacillin 2g/tazobactam 0.5 g is as effective as imipenem 0.5 g/cilastatin 0.5 g for the treatment of acute complicated pyelonephritis and complicated urinary tract infections. Int J Antimicrob Agents 2002; 19: 95-103.
11. Keating GM, Perry CM. Ertapenem: a review of its use in the treatment of bacterial infections. Drugs 2005; 65: 2151-2178.