Clinical Efficacy of Ertapenem for Recurrent Cystitis Caused by Multidrug-Resistant Extended-Spectrum β-Lactamase-Producing Escherichia coli in Female Outpatients

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Purpose: To evaluate the clinical outcomes of ertapenem administered as an outpatient parenteral antibiotic therapy for intractable cystitis caused by extended-spectrum β-lactamase (ESBL)-producing Escherichia coli.

Materials and Methods: We retrospectively reviewed a case series of 3 years of therapeutic experience with ertapenem for intractable recurrent cystitis caused by ESBL-producing E. coli. Ertapenem 1 g/d was parenterally administered to the patients on an outpatient basis until the acquisition of symptomatic improvement and negative conversion of urine culture. Demographic and clinical characteristics of patients, antimicrobial resistance, and clinical response data were analyzed from the patients’ medical records.

Results: During the course of this study, a total of 383 patients were diagnosed with cystitis, and 24 of them showed ESBL-producing E. coli (6.26%). The mean treatment duration of all patients was 8.5 days. The early clinical and microbiological cure rates 0 to 7 days after the end of treatment were 91.7% (22/24) and 90.9% (20/22), respectively. The late clinical and microbiological cure rates 4 to 6 weeks after the end of treatment were 72.2% (13/18) at both time points.

Conclusions: Parenteral ertapenem treatment can be an effective and well-tolerated treatment option for intractable recurrent cystitis by multidrug-resistant ESBL-producing E. coli.

Keywords: Bacterial multiple drug resistance; Beta-lactams; Cystitis; Ertapenem; Escherichia coli

INTRODUCTION

Urinary tract infections (UTIs) are very common bacterial infections, with a global incidence of over 250 million cases per year [1]. Most UTIs are uncomplicated infections in women. About one-third of all women may have at least one episode of uncomplicated cystitis in their lifetime [2]. In clinical practice, uncomplicated cystitis is usually managed with empirical oral antimicrobials on an outpatient basis, because the causative microorganism is generally predictable in healthy women [3].

Extended-spectrum β-lactamases (ESBLs), which can be produced by Enterobacteriaceae, are enzymes that can confer resistance to most β-lactam antibiotics. The incidence of infection with ESBL-producing bacteria has been increasing worldwide [4]. ESBL-producing bacteria typically show cross-resistance to fluoroquinolones and other antimicrobial agents, and therefore, the choice of the appropriate empirical therapeutic regimen may be challenging. Intractable recurrent cystitis caused by ESBL-producing Escherichia coli is considered a complicated UTI. In this setting, patients may have persistent symptoms and unresolved or persistent bacteriuria, despite empirical oral antibiotic treatments [5,6]. Parenteral
carbapenem has recently been considered as the treatment of choice for ESBL-producing bacterial infections [7,8]. Therefore, patients should be in a hospital to complete their antibiotic therapy, even if they are clinically stable and ambulatory, which results in increased costs and length of stay.

Hence, we examined the clinical and microbiological outcomes associated with outpatient ertapenem therapy among female patients with community-acquired cystitis due to ESBL-producing *E. coli* and in whom empirical oral antibiotic therapy had failed. To our knowledge, this is the first study on the use of ertapenem to treat cystitis in female patients with failed empirical treatments owing to ESBL-producing *E. coli*.

**MATERIALS AND METHODS**

We retrospectively reviewed 24 cases of female cystitis caused by ESBL-producing *E. coli* and treated by once daily ertapenem injection therapy between January 2010 and December 2012. The demographic and clinical characteristics of the patients, including complicating risk factors, any antibiotics used in the past 6 months, the empirical antibiotics used to treat this episode, the treatment duration of ertapenem, clinical outcomes, microbiological outcomes, and antibiotic susceptibility, were analyzed from the patients' medical records. Our study and research were done with the Helsinki Review Board of the author's institute and with the patients' medical records. Our study and research were done in accordance with the ethical standards of the Institutional Review Board of the author's institute and with the Helsinki Declaration.

All patients had lower urinary tract symptoms (LUTS), pyuria (>5/high power field in the urine analysis), and culture-proven ESBL-producing *E. coli* in the urine (>10^5 colony-forming units/mL). Patients with systemic symptoms such as leukocytosis, flank pain, and fever; patients requiring hospitalization owing to limited mobility; and patients with chronic indwelling catheters were excluded from this study. The identification of the strains and the antimicrobial susceptibility test were conducted by using the Vitek II system (bioMerieux, Durham, NC, USA).

Ertapenem (Invanz) 1 g/d was parenterally administered to the patients on an outpatient basis until the acquisition of symptomatic improvement and negative conversion of urine culture. Patients were asked to report their symptoms every day. Follow-up urine culture was done when the patients became asymptomatic and near 1 week after the start of treatment. When the patients still had remnant symptoms or positive urine culture results 7 days after the initial treatment, we maintained the treatment for the next 7 days while waiting for the acquisition of symptomatic improvement and negative conversion of urine culture.

Clinical and microbiological outcomes were assessed twice: within 7 days (early) and 4 to 6 weeks (late) after the end of therapy, respectively. Clinical cure was defined as disappearance of the LUTS and microbiological cure was defined as a sterile urine culture.

To compare the groups with and without complicating risk factors, statistical analyses were performed by use of the Fisher exact test and Mann-Whitney U test based on IBM SPSS ver. 18.0 (IBM Co., Armonk, NY, USA). Values of p < 0.05 were considered significant.

**RESULTS**

During the course of this study, a total of 383 patients were diagnosed with cystitis, and 24 of them showed ESBL-producing *E. coli* (6.26%). In terms of the antibiotic susceptibility pattern of the ESBL-producing *E. coli*, only one subject (4.5%) showed susceptibility to fluoroquinolone, and all the subjects (100%) showed susceptibility to amikacin and carbapenem. Fourteen isolates (63.6%) were susceptible to amoxicillin/clavulanate, which had the highest coverage among the oral agents (Table 1).

Table 2 displays the characteristics of ertapenem treatment for recurrent cystitis caused by ESBL-producing *E. coli*. The mean age of the 24 female patients was 47.1 years (range, 22–76 years). Thirteen had complicating risk factors, the most common of which were diabetes (n=5, 20.8%), urological operation and kidney transplantation (n=4, 16.7%), and neurologic disease (Parkinson disease) and short-term Foley catheter indwelling (n=1, 4.2%). Eleven patients did not have complicating factors. When the 13 patients who had complicating factors and the 11 patients who did not were compared, no significant differences were observed in their early clinical outcomes (100% vs. 84.6%, p=0.482), microbiological outcomes (100% vs. 66.7%, p=0.481), or mean treatment duration (8.1±3.5 days vs. 8.9±3.5 days, p=0.093).

The most frequently used antibiotic in the past 6 months was ciprofloxacin (n=21, 87.5%), third-generation cephalosporins (n=5, 20.8%), and carbapenem (n=4, 16.7%) in terms of the antibiotic susceptibility pattern of the ESBL-producing *E. coli*.

**Table 1. Antibiotic susceptibility patterns of ESBL-producing *Escherichia coli***

| Antimicrobial          | No. of susceptible isolates (%) |
|------------------------|-------------------------------|
| Oral agent available   |                               |
| TMP/SMX                | 6/22 (27.2)                   |
| Quinolone              | 1/22 (4.5)                    |
| Ciprofloxacin          | 1/13 (7.7)                    |
| Levofoxacin            | 0/9 (0)                       |
| Amoxicillin/clavulanate| 14/22 (63.6)                  |
| Ampicillin             | 0/22 (0)                      |
| Parenteral agents only |                               |
| Carbapenem             | 22/22 (100)                   |
| Imipenem               | 22/22 (100)                   |
| Meropenem              | 13/13 (100)                   |
| Ertapenem              | 9/9 (100)                     |
| Cefazidime             | 0/22 (0)                      |
| Cefotaxim              | 0/22 (0)                      |
| Piperacillin/tazobactam| 11/22 (50.0)                  |
| Amikacin               | 22/22 (100)                   |

ESBL, extended-spectrum β-lactamases; TMP/SMX, trimethoprim/sulfamethoxazole.

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| Patient | Age (y) | Complicating factors | Used antibiotics prior to ertapenem within 6 months (d) | Used empirical antibiotics to treat this episode (d) | Subdivision of causes of recurrence | Treatment duration of ertapenem (d) | Early clinical outcome | Early microbiologic outcome | Late clinical outcome | Late microbiologic outcome |
|---------|---------|-----------------------|-------------------------------------------------------|-----------------------------------------------|-------------------------------|---------------------------------|-----------------|--------------------------|-----------------|--------------------------|
| 1       | 22      | KT                   | Ciprofloxacin (9), Meropenem (10)                     | Ciprofloxacin (5)                            | Reinfection                   | 5                              | Cure            | Cure                     | Cure            | Cure                     |
| 2       | 56      | None                 | Ciprofloxacin (7)                                    | Ciprofloxacin (7)                            | Unresolved                    | 5                              | Cure            | N/A                      | Failure         | Failure                  |
| 3       | 26      | None                 | Ciprofloxacin (10)                                   | Ciprofloxacin (4)                            | Reinfection                   | 6                              | Cure            | Cure                     | Cure            | Cure                     |
| 4       | 44      | None                 | None                                                  | Levofloxacin (5)                             | Unresolved                    | 13                             | Cure            | Cure                     | Cure            | Cure                     |
| 5       | 54      | None                 | Levofloxacin (14)                                    | None                                         | None                          | 14                             | Cure            | N/A                      | N/A             | N/A                      |
| 6       | 22      | KT                   | Ciprofloxacin (14), Cefotaxim (4), Meropenem (10), Imipenem (6) | Ciprofloxacin (5)                            | Unresolved                    | 5                              | Cure            | Cure                     | Cure            | Cure                     |
| 7       | 60      | None                 | None                                                  | Ciprofloxacin (5)                            | None                          | 6                              | Cure            | Cure                     | N/A             | N/A                      |
| 8       | 59      | DM                   | Ciprofloxacin (14)                                   | Ciprofloxacin (5)                            | Unresolved                    | 5                              | Cure            | Cure                     | Cure            | Cure                     |
| 9       | 23      | Congenital single kidney, pyeloplasty            | Ciprofloxacin (4), Flumoxef (2), Cefcapene (15)      | Cefcapene (4)                              | Unresolved                    | 13                             | Failure         | Failure                   | Cure            | Cure                     |
| 10      | 49      | KT                   | Amikacin (20), Amoxicillin/clavulanate (7), Cefdinir (8) | Ciprofloxacin (9)                            | Reinfection                   | 7                              | Cure            | Cure                     | Failure         | Failure                  |
| 11      | 40      | None                 | Ciprofloxacin (12), Cefcapen (11), Levofloxacin (18) | None                                        | Relapsing                     | 12                             | Cure            | Cure                     | Failure         | Failure                  |
| 12      | 21      | None                 | Ciprofloxacin (22), Meropenem (13), TMP/SMX (27)     | Ciprofloxacin (3)                            | Unresolved                    | 5                              | Cure            | N/A                      | N/A             | N/A                      |
| 13      | 57      | None                 | Ciprofloxacin (14), Levofloxacin (14), Amoxicillin/clavulanate (7) | Cefcapene (14)                              | Reinfection                   | 7                              | Cure            | Cure                     | Cure            | Cure                     |
| 14      | 53      | Urthral caruncle Op  | Ceftriaxon (3), Cefixime (8)                          | Ciprofloxacin (8)                            | Unresolved                    | 5                              | Failure         | Failure                   | Cure            | Cure                     |
| 15      | 45      | Sling Op             | Ciprofloxacin (6)                                    | Cefixime (14)                               | Reinfection                   | 7                              | Cure            | Cure                     | Cure            | Cure                     |
| 16      | 51      | KT                   | Cefixim (12), Cefotaxim (19), Ciprofloxacin (10), Piperaicin/tazobactam (5) | None                                        | Relapsing                     | 16                             | Cure            | Cure                     | Failure         | Failure                  |
| 17      | 27      | None                 | Ciprofloxacin (9), Cefcapene (10)                    | Cefcapene (5)                                | None                          | 10                             | Cure            | Cure                     | Cure            | Cure                     |
| 18      | 52      | Sling Op             | Ceftriax (5), Ciprofloxacin (19), Levofloxacin (22)  | Cefdinir (12)                               | Unresolved                    | 11                             | Cure            | N/A                      | Failure         | Failure                  |
| 19      | 58      | None                 | Ciprofloxacin (5)                                    | Cefcapene (13)                               | Unresolved                    | 4                              | Cure            | Cure                     | Cure            | Cure                     |
| 20      | 52      | DM                   | Amikacin (22), Amoxicillin/clavulanate (13), Imipenem (15) | Cefcapene (13)                              | Unresolved                    | 8                              | Cure            | Cure                     | Cure            | Cure                     |
| 21      | 41      | None                 | Ceftriax (7), Levofloxacin (12)                      | Ciprofloxacin (6)                            | Unresolved                    | 7                              | Cure            | Cure                     | Cure            | Cure                     |
| 22      | 76      | DM                   | Ciprofloxacin (13)                                   | None                                        | Relapsing                     | 7                              | Cure            | N/A                      | N/A             | N/A                      |
| 23      | 72      | DM, Foley catheter  | Ciprofloxacin (4), Ceftriax (8)                      | None                                        | Relapsing                     | 14                             | Cure            | N/A                      | N/A             | N/A                      |
| 24      | 71      | DM, Parkinson disease | None                                                  | Ciprofloxacin (6)                            | Unresolved                    | 10                             | Cure            | N/A                      | N/A             | N/A                      |

ESBL, extended-spectrum β-lactamases; KT, kidney transplantation recipient; DM, diabetes mellitus; TMP/SMX, trimethoprim/sulfamethoxazole; Op, operation; N/A, not assessed.
Clinical Efficacy of Ertapenem for Recurrent Cystitis

lsopin (n=16, 66.7%), levofloxacin (n=7, 29.2%), carbapenem (n=6, 25%), amoxicillin/clavulanate (n=3, 12.5%), amikacin (n=2, 8.3%) and trimethoprim/sulfamethoxazole, piperacillin/tazobactam, and fosfomycin (n=1, 4.2%).

The mean treatment duration of all patients was 8.5 days. The early clinical and microbiological cure rates at 0 to 7 days after the end of the treatment were 91.7% (22/24) and 90.9% (20/22), respectively. Of the 2 clinically failed patients, progression to pyelonephritis occurred in one patient (no. 14) during treatment and she was admitted to a hospital. The other patient (no. 9) was proved to have an inflammatory mass near the urethral orifice and was completely cured after excision of the mass. The late clinical and microbiological cure rates 4 to 6 weeks after the end of treatment were 72.2% (13/18) in both.

Causes of recurrent cystitis in this study could be divided into three categories. These were relapsing infection (symptomatic recurrent UTIs with the same organism following adequate therapy), reinfection (recurrent UTIs with previously isolated bacteria after treatment and with a negative intervening urine culture, or a recurrent UTI caused by a second bacterial isolate), and unresolved infection (the first proven ESBL-producing bacteriuria not responding to initial empirical antibiotic treatment).

Of the 24 patients with recurrent cystitis, unresolved bacteriuria was most frequently observed in 13 (54.2%), followed by reinfection in 6 (25%) and relapse in 5 (20.8%). The group with relapsing infection seemed to have a longer treatment duration, more complicating factors, a lower late clinical cure rate, and a higher rate of late bacteriologic recurrence (Table 3).

Regarding adverse events, only two patients had mild transient nausea, which did not require discontinuation of therapy. No serious adverse events were reported in this study.

**DISCUSSION**

UTI is a widely prevalent infective disease globally, and more than 70% of cases are infective by *E. coli* [2]. Recently, the increase in ESBL-producing *E. coli* has become a global concern [9-11]. In the 2010 report of the Korean Antimicrobial Resistance Monitoring System, the incidence of ESBL-producing *E. coli* was 9.5% (116/1226) in community-acquired infections and 25% (9/36) in hospital-acquired infections [12]. In another report of the Korean Association of Urogenital Tract Infection and Inflammation, the prevalence of ESBL-producing *E. coli* that were isolated from female patients with uncomplicated cystitis was stated as 11.8% [13].

The recent Korean clinical guidelines for UTI recommend fluoroquinolone, β-lactam antibiotics, fosfomycin, and nitrofurantoin (NFT) for the empirical treatment of uncomplicated cystitis [14]. However, in the ESBL-producing state, third-generation cephalosporins are presumed clinically ineffective, regardless of the antimicrobial susceptibility results. Also, the plasmids encoding ESBLs carry gene-encoding resistance to other classes of antibiotics [15,16]. Therefore, the treatment options for ESBL-producing organisms are extremely limited, and it is almost impossible to choose suitable oral antibiotics. This study demonstrated that only one ESBL-producing strain (1/22, 4.5%) was susceptible to fluoroquinolones. Interestingly, susceptibility to amoxicillin/clavulanate was 63.6%, which was highest among other oral agents in this study. It appears that studies on the effectiveness of amoxicillin/clavulanate in ESBL-associated infection are needed in the near future.

There have been limited studies of available oral antibiotics for ESBL-producing *E. coli* infection. In a systemic review of fosfomycin, the antimicrobial susceptibility of fosfomycin in 1657 *E. coli* isolates that produced ESBL was shown to be 96.8% (1,604/1,657) [17]. In two studies that evaluated oral treatment with fosfomycin, the cumulative clinical cure rate of fosfomycin treatment was 93.8% (75 of 80 patients) [9,18]. However, one of these studies had a lower rate of microbiological success (41 of 52, 78.8%) [18]. Furthermore, as far as we know, antimicrobial susceptibility testing of fosfomycin in gram-negative bacteria is unavailable in Korea, because the standard susceptibility cards that are used in most Korean hospitals and institutes do not contain fosfomycin. With regard to the effect of NFT on ESBL-producing *E. coli* related to lower-level UTI, a study published in 2012 showed that all isolates were susceptible to NFT and the overall clinical and microbiological success rates were 69% (52/75) and 68% (51/75) [19]. However, in Korea, oral NFT is not produced and its sus-

**Table 3. Patient characteristics according to subdivision of causes of recurrence**

| Subdivision of causes of recurrence | No. | Mean treatment duration (d) | Presence of complicating factor (%) | Early clinical cure rate | Early microbiologic cure rate | Late clinical cure rate | Late microbiologic cure rate |
|------------------------------------|-----|-----------------------------|-------------------------------------|--------------------------|-------------------------------|------------------------|----------------------------|
| Unresolved                         | 13  | 8.5                         | 5/13 (38.4)                         | 11/13 (84.6)             | 9/11 (81.8)                   | 7/9 (77.7)            | 7/9 (77.7)               |
| Relapsing                          | 5   | 10.8                        | 4/5 (80.0)                          | 5/5 (100)                | 5/5 (100)                     | 1/3 (33.3)            | 1/3 (33.3)               |
| Reinfection                        | 6   | 6.5                         | 4/6 (66.7)                          | 6/6 (100)                | 6/6 (100)                     | 5/6 (83.3)            | 5/6 (83.3)               |

Values are presented as number (%).
ceptibility testing is unavailable. Therefore, efforts to find suitable oral antibiotics for the treatment of ESBL-producing bacterial infections are required in Korea.

There is no doubt that the treatment of choice for critical infections caused by ESBL-producing gram-negative bacteria is parenteral carbapenem [8,20]. However, in the case of simple cystitis without systemic symptoms, for which treatments fail due to ESBL-producing E. coli, the use of carbapenem such as imipenem or meropenem could pose a dilemma, because the three to four times daily parenteral treatments require hospitalization, which results in increased cost and time.

Ertapenem is a parenteral and long-acting carbapenem. It is more highly protein-bound and has a longer half-life than does imipenem or meropenem. Its longer half-life and once-daily parenteral dosage of 1 g make it an ideal choice for outpatient parenteral antibiotic therapy [21]. It has been shown to have good in vitro activity against ESBL-producing Enterobacteriaceae. However, ertapenem has limited activity against isolates of nonfermentative gram-negative bacilli such as Pseudomonas aeruginosa and Acinetobacter spp. and is the least active carbapenem against enterococci [22]. Ertapenem should not be used empirically to treat patients with nosocomial infection because Pseudomonas aeruginosa and other nonfermentative gram-negative bacilli are likely pathogens in this setting.

Despite the few observational data regarding clinical outcomes with ertapenem, recent studies reported the clinical efficacy of ertapenem in the treatment of ESBL-producing infections [23-25]. In this study, all 24 ESBL strains were found to be susceptible to carbapenem. Overall, its early clinical and bacterial efficacies were 91.7% (22/24) and 90.9% (20/22), respectively. The results were comparable to the following expected clinical and microbiological efficacies of common oral agents for acute uncomplicated cystitis, which were described in the 2010 update of the guidelines for the treatment of acute uncomplicated UTIs in women by the Infectious Diseases Society of America: NFT (100 mg twice daily for 5-7 days, 93% and 88%), fluoroquinolones (the dose varies by agent, 3-day regimen, 90% and 91%), and trimethoprim/sulfamethoxazole (160/800 mg twice daily for 3 days, 93% and 94%), respectively [26]. However, the late clinical and bacterial efficacies dropped to 72.2%, which was especially predominant in relapsing infection (33.3%). Physicians should understand this fact before treatment and future studies should focus on the management of relapsing infection due to bacterial persistence.

The main limitation of this study was the fact that it was a retrospective study with a relatively small number of cases but was not a randomized or controlled study. Different treatment duration and irregular follow-up may disturb exact interpretation. In addition, because this was a retrospective study, we did not have control cultures for all cases.

The results of this study suggest that patients with recurrent cystitis caused by ESBL-producing E. coli, with no suitable oral antibiotic therapy, can be treated effectively as outpatients with once-daily parenteral ertapenem.

CONCLUSIONS

The emergence of and gradual increase in multidrug-resistant ESBL-producing E. coli have become global threats to human health. The choice of suitable oral antibiotics is extremely limited in the ESBL-producing state. Finding regionally useful oral antibiotics that are effective against UTIs caused by ESBL-producing E. coli should be of high priority. The administration of once-daily parenteral ertapenem to outpatients may be a useful secondary therapeutic option for recurrent cystitis caused by ESBL-producing E. coli in patients in whom empirical oral antibiotic treatment has failed.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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