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Original Article

Ertapenem For The Treatment Of Complicated Urinary Tract Infections Caused By Extended-Spectrum B-Lactamase-Producing Bacteria: A Case Series Report

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Abstract

Urinary tract infections with extended-spectrum β-lactamases (ESBL) are an increasing public health concern. We evaluated our experience with the use of ertapenem for complicated urinary tract infections (cUTI) caused by ESBL- producing bacteria. Sixty-four patients aged >18 years who had a cUTI caused by ESBL- producing microorganisms that were treated with ertapenem at Sisli Etfal Training and Research Hospital, from January 1st, 2010 to December 31st, 2011, were included in this study. Data on patients demographic, clinical and laboratory results were collected. The median age was 65.8 years (range, 30 to 95). All patients had at least one risk factor complicating factor except two of them. The most common underlying problem was prior antibiotic exposure. The pathogens isolated from urine samples were ESBL-producing E. coli in 49, ESBL-producing K. pneumoniae in 12 and ESBL-producing K. oxytoca in 2 patients. All were susceptible to ertapenem in vitro. The average duration of ertapenem therapy was 14±4 days for upper UTI and 11±2 days for lower UTI. All patients achieved clinical cure and bacteriological eradication in urine. One patient had relapse and six of them had reinfection. Only one case had diarrhea which did not require discontinuation of therapy. Our results demonstrate that ertapenem is suitable for the treatment of cUTI cause by ESBL-producing bacteria.

Introduction

Urinary tract infection is the most common bacterial illness occurring in adults (1). Urinary tract infections (UTIs) are among the most prevalent infectious diseases in the general population, with an estimated overall incidence of 18/1000 person per year. UTIs are classified into complicated and uncomplicated regardless of the site and severity of the infection (2). The distinction between an uncomplicated UTI and a complicated UTI is important because of implications to pre- and post-treatment evaluation and the type and duration of antimicrobial regimens. Complicated UTI (cUTI) is characterized by the presence of structural abnormalities (e.g. urinary obstructions), metabolic and/or hormonal abnormalities (diabetes mellitus, pregnancy, renal impairment, etc.), and impaired host responses (transplant recipients, neutropenic patients, etc.) (3).

There are a number of sequela from complicated UTIs that may have serious or fatal consequences (4). Therefore, patients with cUTIs require more diagnostic testing, broad-spectrum empiric antimicrobial therapy, and a longer duration of treatment (2).

Extended-spectrum β-lactamases (ESBLs) are enzymes that confer resistance to most β-lactam antibiotics. ESBL- producing bacteria also typically show increased levels of resistance to other agents and therefore treatment options are often limited. Over the past 10 years there has been an increase in incidence of infections due to ESBL- producing organisms globally (5).

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A recent report from the Infectious Diseases Society of America listed ESBL-producing Klebsiella spp and E coli as one of the six drug-resistant microbes to which new therapies are urgently needed (6).

Ertapenem is a parenteral broad spectrum carbapenem that was used to once daily. It is approved for the following infections: complicated intra-abdominal infections, complicated skin and skin-structure infections , acute pelvic infections, complicated urinary tract infections and community-acquired pneumonia and for the prophylaxis of surgical-site infection following elective colorectal surgery in adult patients. It is active against many Gram-positive and negative bacteria, including several anaerobic organisms but has a narrower spectrum of antimicrobial activity, compared with older carbapenems (7). Ertapenem is active against ESBL-producing Enterobacteriaceae in vitro (8). However there are no randomized controlled trials of therapy for complicated UTI caused ESBL- producing bacteriae (9). The objective of our case series was to examine the clinical and microbiologic outcomes and relapses associated with ertapenem treatment of patients with complicated UTI caused ESBL producing bacteria.

Material and Methods

Sixty-four patients aged >18 y who had a cUTI caused by ESBL-producing microorganisms that was treated with ertapenem at the Sisli Etfal Training and Research Hospital, from 1 January 2010 to 31 December 2011, were included this study. In this retrospective study, the patients were detected through the hospital's pharmacy records by screening the antibiotic prescriptions used.

Relevant parameters such as patient characteristics, underlying diseases, clinical manifestations, laboratory and radiological test results, and treatment modalities used before ertapenem treatment, were evaluated.

In the case of an indwelling urinary catheter, diabetes mellitus, neurogenic bladder, obstruction due to nephrolithiasis, tumour or fibrosis, urinary retention due to benign prostatic hypertrophy, bladder cancer or other urological anatomical abnormalities were considered to be complicated (10).

UTIs were confirmed by positive urine cultures and quantitative bacterial counts. If septicemia secondary to a UTI was suspected, appropriate blood samples were obtained for culture before treatment.

Urine specimens were Gram-stained, and causative pathogens isolated by culture were identified by Standard microbiological techniques in our microbiology laboratory. The isolates were tested for susceptibility to ertapenem. The susceptibility was determined by disk diffusion test on Mueller – Hinton agar according to the methodology and inhibition zone diameters recommended by the Clinical and Laboratory Standards Institute (11). ESBL was detected by modified double-disk synergy test with cefotaxime and ceftazidime disks (Becton Dickinson, Sparks, MD, USA) on opposite sides of an amoxicillin/clavulanic acid disk at 25 mm apart.

Clinical assessments, laboratory tests and cultures taken were repeated during antibiotic treatment and follow-up.

Patients received ertapenem 1g once a day (Invanz; Merck & Co., Inc.) intravenously with a 30 min infusion. If creatinine clearance was <30 mL/min/1.73 m2, dose adjustment made 500mg once a day.

Criteria for response: Clinical success was defined as resolution of symptoms on the control visit, and microbiological success was defined as a sterile control urine culture performed 7-9 days after the last dose of the drug in accordance with the Infectious Diseases Society of America (IDSA) guidelines (12). Superinfection was defined as the isolation of one or more new pathogens from urine at shortterm follow-up (13). Relapse was defined as isolation of the pretreatment pathogen in the control urine cultures performed 28-31 days after the end of therapy. Reinfection was defined as any pathogen in the control urine cultures performed 28-31 days after the end of therapy (14).

We performed descriptive statistical methods to demonstrate demographic and basic clinical features. Statistical analysis was performed using Stata SE/12. (StataCorp LP, Texas USA).

Results

Sixty-four patients with median age of 65.8±14.4years (range, 30 to 95) were assessed. The demografic and clinical data are shown in table 1.

The average total length of hospital stay was 22 days. (Range: 7- 50 days) All patients had at least one risk factor complicating factor except two. The most common underlying problem was prior antibiotic exposure. Forty three patients had more than one complicating factor. The laboratory results of the patients are shown in table 2.

If septicemia secondary to a UTI was suspected,

appropriate blood samples were obtained for culture before treatment. Eighteen patients had positive blood cultures and the isolated microorganisms were: E.coli:13, Klebsiella pneumoniae:3, Klebsiella oxytoca:1, Enterobacter cloacae:1. The microorganisms isolated from urine samples are shown in table 3.

All pathogens were resistant to ciprofloxacin and TMP-SXT but were susceptible to ertapenem, imipenem/cilastatin and meropenem. Therapy was switched to ertapenem in thirty six patients after obtaining the urine culture results. Among these patients 24 of them previously received beta lactam-beta lactamase combination, 4 other carbapenems, 8 ceftriaxone. Thirteen patients had glomerular filtration rate (GFR) < 30 ml/min and all of them received ertapenem as 500 mg daily. Eleven patients were on haemodialysis. The average duration of ertapenem therapy was 14±4 days for upper UTI and 11±2 days for lower UTI. All patients achieved clinical cure and bacteriological eradication in urine.

Two patients developed secondary infection. One patient had malignancy involving the urinary tract, nephrostomy tube and previously received imipenem. This patient had upper urinary tract infection caused by Acinetobacter baumanii which developed on the tenth day of ertapenem therapy. The other patient had upper urinary tract infection caused by Enterococcus spp. These two patients had treatment modifications. Relapse appeared in only one patient. This patient had risk factors as older age, prostatic hypertrophy and long-term indwelling catheter. Six patients had reinfection and two of them developed colonization after stopping the treatment. Only one case had diarrhea which did not require discontinuation of therapy.

Table 1. Demografic and clinical data of the patients.

Characteristic	Number of patients (%)
Mean age (range) years	65.8 (30-95)
Male	41 (64)
Prior hospitalization within last 3 months	34 (53)
Long-term indwelling catheter	23 (35)
Clean intermittent catheterization	4 (6)
Prior antibiotic exposure	52 (81)
Diabetes mellitus	15 (23)
Cardiac disease	5 (8)
Malignancy involving the urinary tract	14 (22)
Pulmonary disease	4 (6)
Nephrolithiasis	13 (20)
Benign prostatic hypertrophy	15 (23)
Nephrostomy tube	3 (5)
Prostate biopsy	4 (6)
Chronic renal failure	13 (20)

Discussion

ESBL- producing Enterobacteriaceae have been reported worldwide, most often in hospital specimens but also in samples from the community (15). Risk factors identified as predictors of ESBL with organisms are prolonged length of hospitalization, underlying disease, urinary catheters, prior exposure to antibiotics, surgical procedures and immunosuppressive therapy (16-18) . Treatment options for patients with infection caused by ESBL-producing Enterobacteriaceae are limited (19). Inadequate ampiric antibiotherapy may cause treatment failure and increase the mortality risk (20) . A parenteral carbapenem is often the only suitable antimicrobial agent (18). Frequent use of carbapenem will probably ensue which may in turn have untoward consequences

Table 2. Laboratory results of the patients.

	n	WBC/mm3	Neutrophil (%)	CRP (folds)
Lower UTI	13	6400±1600	63±20	5±3
Upper UTI	51	16,200±8500	84±10	23±13

Table 3. The microorganisms isolated from urine samples.

	E.coli	K. pneumoniae	K. oxytoca	Culture negative samples
Lower UTI	9	4	0	0
Upper UTI	40	8	2	1
Total	49	12	2	1

on the prevelence of resistance to these antibiotics in microorganisms (21).

Ertapenem is a broad-spectrum carbapenem and ideal choice for outpatient parenteral antibiotic therapy (OPAT) because of its once daily parenteral dosage. It has been shown to have good in vitro activity againist ESBL producing bacteria (22). There are few observational studies with ertapenem for the treatment of infections caused by ESBL producing organisms. Firstly, Teng at al in 2007 showed excellent efficacy of ertapenem for the treatment of ESBL producing gram negative bacterial infections, comparable with either imipenem or meropenem (23). Melody Berg at al in 2008 showed successful clinical and microbiological results with ertapenem consolidation therapy (19).

Recent studies suggest that the treatment of ESBL-producing E. coli or Klebsiella bacteriemias with ertapenem was as effective as imipenem or meropenem when compared with the terms of mortality and microbiological response (24).

ESBL production by Enterobactericeae family is increasing in studies reported from Turkey. Infections caused by ESBL producing microorganisms are a serious problem in a Teaching and Research hospital with 800 beds like ours. In a study conducted at our hospital in 2009 it was found that 19.7% of Klebsiella spp and 11.5% of E.coli produce ESBL (25). In a previous study from our hospital it was reported that treatment of UTI caused by ESBL producing bacteria with ertapenem had favorable clinical response (26).

In our study, ertapenem was well tolerated and all patients achieved clinical cure, one patient had relapse and six of them had reinfection.

Previous studies have illustrated that prior use of imipenem or meropenem is associated with colonization or infection due to multidrug resistant A. baumannii, P. aeruginosa (27). Ertapenem has limited activity againist A. baumannii and P. aeruginosa. It is still controversial whether the usage of ertapenem has an impact on the susceptibility patterns of P.aeruginosa to other carbapenems. Reports of the development of carbapenem resistance during carpapenem therapy, including ertapenem, are concerning (28). In our study resistance to ertapenem was not observed to have developed during therapy.

In conclusion, ertapenem is suitable the treatment of ESBL producing cUTI. (Because of effective, lower cost, feasibility in outpatient parenteral antibiotic therapy and potential benefit in reducing carbapenem resistance in A. baumanii and P. aeruginosa). Further prospective randomised controlled studies are needed.

Declaration of Interest: We state that there is no conflict of interest.

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