Research Article

Effectiveness of Ertapenem in treatment of ESBL producing Enterobacterial UTI

Rajeev T P

Professor, Department of Urology, KS Hegde Medical Academy, Nitte University, Mangalore-575018, Karnataka, INDIA.
Email: rajeevtp@yahoo.com

Abstract

Introduction: Extended Spectrum Beta Lactamase (ESBL) producing gram negative bacterial urinary tract infections (UTI) are an emerging threat in clinical practice. Carbapenem classes of drugs are the treatment of choice for ESBL infections. This study is on the clinical and microbiological effectiveness as well as the benefits of Ertapenem, a carbapenem derivative in ESBL producing bacterial UTI. **Materials and Methods**: This is a prospective study on 40 patients who were treated with Ertapenam for UTI at K.S. Hegde hospital, Mangalore from May 2010 to January 2014. These patients had clinically symptomatic UTI, culture positive for ESBL producing gram-negative bacteria and with moderate risk disease. Injection Ertapenam was given as 1 gm once a day intra-venously for a minimum period of 10 days and the clinical and microbiological response rate were assessed. **Results**: 34 patients were cured. Outcome of 2 patients were undetectable as they did not consent for continuing Ertapenem due to financial constraints. 2 patients had poor clinical response and worsening of vital parameters. Remaining two cases required different antibiotics during the course of treatment as repeat culture showed drug resistance or a different species of bacteria. **Conclusions**: Ertapenem is highly effective in treatment of moderately severe ESBL producing gram-negative UTI, excepting Pseudomonas. It shows excellent response to E. coli and Klebsiella species. Being single a dose, it has better patient compliance. The treatment is cost effective compared to other carbapenems.

Keywords: Ertapenem, ESBL, Gram-negative bacteria, UTI, effectiveness.

***Address for Correspondence:**
Dr. Rajeev T. P., Professor, Department of Urology, KS Hegde Medical Academy, Nitte University, Mangalore-575018, Karnataka, INDIA.
Email: rajeevtp@yahoo.com

Received Date: 08/04/2015 Revised Date: 20/04/2015 Accepted Date: 24/04/2015

Access this article online	
Quick Response Code:	Website: www.statperson.com
	DOI: 27 April 2015

INTRODUCTION

Extended Spectrum Beta Lactamase (ESBL) producing gram negative bacterial urinary tract infection (UTI) is an emerging threat in current clinical practice. They are a growing concern especially in hospitalized patients. Recent data suggest that ESBL producing bacteria are a rising cause for community acquired urinary infections too. ESBL infections are associated with higher mortality, increased cost and therefore pose a significant challenge in healthcare sector. Traditionally these infections can be effectively treated by carbapenem class of drugs, making them the drug of choice for ESBL infections. This study is on the clinical and microbiological effectiveness as well as the benefits of Ertapenem, a carbapenem derivative in ESBL producing bacterial UTI. Ertapenem, with a narrow spectrum of activity has a lower inhibitory concentration against these organisms making it a very promising first line drug. Existing data suggest high clinical response with Imipenem and Meropenem (about 80-100%), hence used as the first line agent. Now, concerns have arisen over maintaining their coverage against Pseudomonas and their potential for selecting multi-drug resistant strains. As increase in number of ESBL infections are observed today, there is a need for a narrower spectrum carbapenem as the first line treatment modality for ESBL. In vitro studies of Ertapenem showed an excellent susceptibility to ESBL producing E. coli and Klebsiella. In comparison with other carbapenems, Ertapenem has an advantage of once a day dosage. The aim of this study is to assess Ertapenem as the first line of treatment option in such cases by determining the clinical response rate and the microbiologic cure rate in our hospitalized patients.

How to site this article: Rajeev T P. Effectiveness of Ertapenem in treatment of ESBL producing Enterobacterial UTI. *International Journal of Recent Trends in Science and Technology* April 2015; 14(3): 725-729 http://www.statperson.com (accessed 28 April 2015).

MATERIAL AND METHODS

This is a prospective study on 40 patients who were treated with Ertapenem for UTI at K.S. Hegde hospital, Mangalore, Karnataka, India from May 2010 to January 2014. The patients included are having clinically symptomatic UTI, urine culture positive for ESBL producing gram-negative bacteria and with moderate risk disease (not in severe septicemia or requiring heamodynamic/ ventillatory/ ICU Support). The clinical features include painful urination, urgency, frequency, tenderness in supra pubic area and fever higher than 38^0 C. About 23 males and 17 females were included in this study. The male patients were aged between 40 to 82 years (mean age 63). The females were aged between 26 to 70 years, with an average age of 53 years. Out of the 40 patients, 26 patients had community onset UTI (65%). The patients with ESBL producing gram-negative urinary tract infection clinically presented with recurrent or persistent UTI. Most of them have received at least 2 or more antibiotics for UTI prior to this study, empirically or culture based. This can be Quinolones, Cephalosporins, Amikacin or Nitrofurantoin, mostly at an outpatient basis. In this study, ESBL producing gram-negative bacteria detected by culture (>10^5 CFU/ml) were E. coli[26], Klebsiella[11], Enterobacter[2], Proteus[2], Acinetobacter[1]. Most common causative organisms were ESBL producing Escherichia and Klebsiella (Chart.1). Two patients had mixed organisms. Co existing fungal UTI were present in 3 patients.

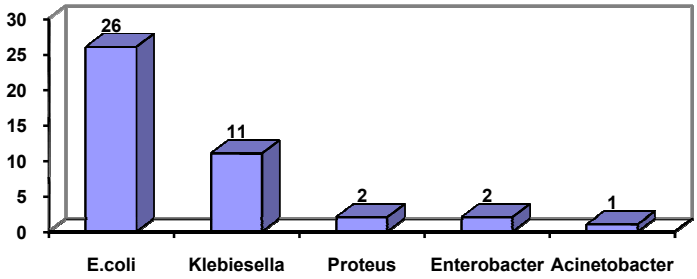

Figure 1: Showing the various bacteria grown in urine culture

The severely septicemic, with hemodynamic instability or those requiring ventillatory supports were preferentially excluded and treated by Imipenem or Doripenem (in consultation with Intensivist or Nephrologist). Injection Ertapenem initiated as 1 gm once a day intra-venously if the culture is suggestive of ESBL producer. No renal titration of dosing were required in our patients, as dose reduction required only when GFR is very low (Creatinine clearance <30 ml/min). Ertapenem was continued for a minimum period of 10 days. On an average the patients have received Ertapenem for a period of 10.6 days (mean). The urine culture and sensitivity was repeated at 7^{th} day. At completion they were switched over to oral Nitrofurantoin 100 mg once a day for 3 months. Some of them had co-morbid medical illness like diabetes mellitus (18 patients), renal impairment (8 patients). Few of them had co existing genito-urinary abnormalities. It can be prostate related events like benign prostatic hyperplasia (4 patients), malignancy of prostate (2 patients) and two with a recent history of trans urethral resection of prostate. Five female patients had meatal stenosis. Urinary diversions like ileal conduit was present in one patient and a nephrostomy in another patient. One patient was a diagnosed case of neurogenic bladder due to spinal trauma. Three patients provided a history of recent upper urinary tract endoscopy.

RESULTS

The clinical response rate and the microbiologic cure rate of patients after receiving the Ertapenem were assessed as a primary end point of this study. Clinical improvement or resolution as measured by the absence of earlier clinical symptoms and changes in previously elevated markers of infection like fever, leucocytosis, and pus cells in urine. 34 patients (85%) were cured of ESBL producing gram-negative bacterial UTI. Majority of them felt better even at 4-5 days of initiation of treatment. Microbiologic cure can be defined as a subsequent negative culture upon completion of Ertapenem therapy. All 34 patients had a sterile culture report at completion of treatment. Outcome of 2 patients were undetectable as they did not consent for continuing Ertapenem due to financial constraints, opted out from the study. If there is lack of improvement in clinical parameters after receipt of Ertapenem for 4 days or switching the regimen to another active antibiotic with in vitro susceptibility is considered as a therapeutic failure. As 2 had poor clinical response and worsening of vital parameters, were shifted to Doripenem. In one case repeat culture on the 7^{th} day

detected multi drug resistant Pseudomonas species. Another patient required Colistin as the re-culture showed sensitivity only for it. No clinical side effects like convulsions, confusion state or any laboratory test abnormalities were viewed in patients during the study period. In later part of study, 9 of the patients received Ertapenem on an out-patient basis after 2-3 days of hospitalization as good clinical response was noted. Thus confirmed the use of Out Patient Parenteral Antibiotic Therapy (OPAT) programme to facilitate early discharge from hospital of patients with ESBL associated UTIs further reducing the cost and length of hospital stay. The per day usage cost of Ertapenem purchased from our hospital pharmacy is approximately Rs.2400. This regimen has a lower cost when compared with other carbapenems (Table: 1).

Table 1: Comparing the cost of treatment of various Carbapenems (Jan 2014, at KS Hegde hospital pharmacy)

Drug	Dosage	Per day cost in rupees
Meropenem	1 gm thrice a day	1250x3=3750
Imipenem+Cilastatin	500mg thrice a day	1595x3=4785
Doripenem	500mg thrice a day	2750x3=8250
Ertapenem	1gm once a day	2400x1=2400

DISCUSSION

The incidences of ESBL producing bacterial infections are increasing world wide. Today an intractable recurrent cystitis caused by ESBL producing E. coli is considered as a complicated UTI. Such patients may have persistence of symptoms and unresolved or persistent bacteria despite empirical oral antibiotic treatments. The enzyme, ESBLs which are produced by Enterobacteriaceae can confer resistance to most beta lactum antibiotics. Carbapenems have recently considered as the drug of choice for ESBL producing bacterial UTI[1]. ESBL infections are associated with increase morbidity, mortality, need for broad spectrum antibiotics and escalating health care costs. Earlier ESBL UTI was seen as a Healthcare Associated Infection (HAI); nowadays, community acquired UTI (CAUTI) is the most common infection caused by ESBL bacteria. Patients diagnosed as having UTI in the outpatient clinic or emergency room or diagnosed within 48 hours of hospitalization were classified as CAUTI and patients diagnosed after 48 hours of hospitalization period were classified as HAI UTI. Today, urinary infection is the most common HAI and the major risk factor for nosocomial UTI is urinary catheterization. Apart from catheter, a history of previous hospitalization, female gender, old age, previous antimicrobial medications, urogenital surgeries are other risk factors for ESBL UTI.[2,3] Identified risk factors for CAUTI are diabetes mellitus[2], recent antibiotic use, traveling to Asia/Middle east, and recreational swimming.[4] Household transmission outweighs HAI and is enhanced by the presence of index patient recently discharged or cared for in a hospital[5]. E. coli is the most widely prevalent organism causing CAUTI with an alarmingly high rate of resistant ESBL species.[2] Klebsiella and Enterococcus faecalis accounts for most of the remaining infections[2,6]. Other predominant pathogens are Pseudomonas aeruginosa, Proteus and candida species[7]. The most common pathogens in this study were E.coli about 65% of cases and Klebsiella as second with 27% incidence. The fecal relative abundance of ESBL producing E.coli (ESBL RA) was linked to the occurrence of community UTI in woman who are not exposed to any antibiotics[8]. Trimethoprim-Sulphamethoxazole (TMP-SMZ) and fluroquinolones are the antibiotic recommended by the Infectious Disease Society of America (IDSA) for urinary tract infections[9]. Despite this, worldwide resistance to fluroquinolones and sulpha drugs in UTI has reported. Ampicillin frequently used as an alternative drug owing to its activity against gram-negative micro-organisms. As acquired resistance to beta lactum antibiotics has reported in microbiological studies, Cephalosporins stable to beta lactamase were developed and this became the choice of antibiotic for UTI[9]. However, after the emergence of ESBL producing microorganisms in Western Europe in mid 1980's, anxiety about bacterial resistance to cephalosporin has been growing more and more[10]. The uropathogens included in this study showed resistance to fluroquinolones, 3rd generation cephalosporins and Piperacillin/Tazobactum combination. They had highest sensitivity to carbapenem and the next best alternative was aminoglycosides, but majority showed no response to Gentamicin and Amikacin in vivo[2]. Of the Carbapenems, Meropenem is more active against enterobacteria and less for gram-positive species and is given at a dose of 500 mg every 8th hourly. Imipenem/Cilastatin drug is more active against gram-negative especially Pseudomonas and Enterococci. This has to be administered every 6 to 8th hourly. Dorepenem at a dose of 500 mg 8th hourly is particularly active against pseudomonas hence for treatment of complicated UTI with septicemia. Ertapenem is a group 1 carbapenem drug with a narrower spectrum of activity. It is active against gram-negative and gram-positive bacteria and has clinical activity against anearobes. The molecule is not active against Pseudomonas, Acinetobacter, Methicillin resistant Staphylococcus aureus (MRSA) and Ampicillin resistant

Enterococci. Hence it cannot be used as an empirical treatment of hospital acquired infections as it lack activity against Pseudomonas. 1 gm Ertapenem was given intravenously over a period of 30 minutes as once a day dose. Ertapenem is highly protein bound hence longer half life of 4-5 hours unlike other Carbapenems which have half life of 1 hour. 80% of the drug is excreted by kidneys hence metabolism by liver is not important, so about dosing. If creatinine clearance >30ml/min, no dosage adjustment is required. In End Stage Renal Disease (ESRD) and severe renal impairment (Cr.Clearence <30 ml/min) a dose of 500 mg/day is given. Confusion state, headache and worsening of convulsions are the side effects, which were reported very rarely. However in case of 'simple' cystitis caused by ESBL producing enterobacteria, the use of Meropenem and Imipenem could pose a dilemma to the clinician because of prescribing the 'antibiotics of last resort'[11], requirement of hospitalization, increased cost and time[3]. In such situations, Ertapenem is an ideal choice, being its long half life, once daily parenteral dosage and can be used as an OPAT. 9 patients in this series had a successful OPAT programme. Fong *et al* reported a clinical response of 78% and a microbiologic cure rate of 92% with Ertapenem in ESBL infections[12]. Nitrofurantoin considered as one of the oldest anti-infective drugs for UTI and surprisingly resistance to this molecule is minimal, even today. The lack of resistance could be due to the multiple mechanisms of actions of Nitrofurantoin, requiring organisms to develop more than a single mutation in order to cause resistance[13]. Similarly; systematic reviews showed the antimicrobial susceptibility of Fosfomycin in E. coli isolates that produces ESBL, is more than 96%[14]. Meanwhile, the orally active beta lactum antibiotic Faropenem is relatively resistant hence not therapeutically approved in many countries. This study has limitations due to the small sample size. During the study period our institutional microbiology laboratory only reports the interpretation of susceptibility and will quantify the minimum inhibitory concentration (MIC) upon request. The treatment is based only on susceptibility report and not including the MIC of Ertapenem in culture. Also, lack of information about the molecular analysis of specific ESBL phenotypes limits the generalization to other institutions. Some ESBL producing strains have now developed very effective ways to deal with carbapenems and there is no treatment alternative for such strains[15]. The carbapenem resistant microorganisms raise a concern over the available options to treat complicated and drug resistant cases. The resistance pattern is ever increasing due to an uncontrolled abuse of available antibiotics. Recently drug resistance to carbapenem among coliforms due to production of New-Delhi Metallo-beta-lactamases (NDM-1)[16] isolated in U.S and U.K from patients received recent medical care in South Asian Countries. To prevent the spread of multi-drug resistant microorganisms, administrative and educational programmes had to develop and to provide appropriate guidelines for prescription of antibiotics and urinary catheterization and to follow these guidelines strictly.

CONCLUSIONS

Ertapenem is a promising drug for the culture guided treatment of ESBL producing gram-negative complicated UTIs. Ertapenem is highly effective in treatment of moderately severe cases, except pseudomonas aetiology. It shows excellent response to E. coli and Klebsiella species. Being single a dose, it has better patient compliance. Renal titration of dosing has to be done only when there is severe impairment of renal function (Cr. Clearance <30 ml/min). The treatment is cost effective compared to other carbapenems. In selected patients Ertapenem can be given as outpatient parenteral therapy which further reduces the cost of treatment.

ACKNOWLEDGMENT

I appreciate the help provided by department of microbiology, KSHEMA and the in-charge pharmacist, KS Hegde Hospital for supporting this study.

REFERENCES

1. Kinal S, Summaya M: Susceptibilities of ESBL-producing Enterobacteriaceae to Ertapenem, Meropenem and Piperacillin-Tazobactum: National Journal of Medical Research. 2012, April: Volume 2(2).
2. Eshwarappa M, Dosegowda R, Aprameya IV, Khan MW, Sivakumar P, Kempegowda P: Clinico-microbiological profile of urinary tract infection in south India: Indian J Nephrol. 2011 Jan-Mar; 21(1): 30–36.
3. Lee DS, Choe HS, Lee SJ, Bae WJ, Cho HJ, Yoon BI *et al*: Antimicrobial Susceptibility Pattern and Epidemiology of Female Urinary Tract Infections in South Korea, 2010-2011: Antimicrob Agents Chemother. 2013 Nov; 57(11): 5384–5393.
4. Søraas A, Sundsfjord A, Sandven I, Brunborg C Jenum PA: Risk Factors for Community-Acquired Urinary Tract Infections Caused by ESBL-Producing Enterobacteriaceae –A Case–Control Study in a Low Prevalence Country: 2013, July DOI: 10.1371/journal.pone.0069581.
5. Hilty M, Betsch BY, Stuber KB, Heiniger N, Stadler M, Kuffer M *et al*: Transmission Dynamics of Extended-Spectrum β-lactamase–Producing Enterobacteriaceae in the Tertiary Care Hospital and the Household Setting: Clin Infect Dis. 2012 Oct 1; 55(7): 967–975.
6. Gupta, S, Kapur S, Padmavathi DV: Comparative Prevalence of Antimicrobial Resistance in Community-Acquired Urinary Tract Infection Cases from

Representative States of Northern and Southern India: Clin Diagn Res. 2014 Sep; 8(9): DC09–DC12
7. Tasbakan MI, Durusoy R, Pullukcu H, Sipahi OR Ulusoy S: Hospital-acquired urinary tract infection point prevalence in Turkey: Differences in risk factors among patient groups: Ann Clin Microbiol Antimicrob. 2013; 12: 31.
8. Ruppe E, Lixandru B, Cojacaru R, Elisabeth P, Angebault C, Visseaux C: Relative Fecal Abundance of Extended-Spectrum-β-Lactamase-Producing Escherichia coli Strains and their Occurrence in Urinary Tract Infections in Women: Antimicrob Agents Chemother. 2013 Sep; 57(9): 4512–4517.
9. Lee DS, Lee CB, Lee SJ: Prevalence and Risk Factors for Extended Spectrum Beta-Lactamase-Producing Uropathogens in Patients with Urinary Tract Infection: Korean J Urol. 2010 Jul; 51(7): 492–497.
10. MukherjeeM, Basu S, Mukherjee SK, Majumder M: Multidrug-Resistance and Extended Spectrum Beta-Lactamase Production in Uropathogenic E. Coli which were Isolated from Hospitalized Patients in Kolkata, India: J Clin Diagn Res. 2013 Mar; 7(3): 449–453.
11. Papp-Wallace KM, Endimiani A, Taracila MA, Bonomo RA: Carbapenam: Past, present and future: Antimicrob. Agents. Chemother. 2011, Nov.55 (11): 4943-60.
12. Fong JJ, Rose L, Radiqan EA: Clinical outcomes with Ertapenam as a first line treatment option of infections caused by ESBL producing gram-negative bacteria: Ann Pharmacother. 2012 Mar, 46(3): 347-52.
13. Babak P, Farzad F, Shima M, Mostafa T, Farah S, Hossein H *et al*: Increase resistant rates and ESBL production between E. coli isolates causing urinary tract infection in young patients from Iran: Braz J Microbiol. 2012 Apr-Jun; 43(2): 766–769.
14. Mathew EF, Antonia CK. Anastasios MK, Drosos EK.: Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum β-lactamase producing, Enterobacteriaceae infections: a systematic review. The Lancet, infectious diseases, 2010, Jan vol 10(1). P43-50.
15. Lee B, Kang SY, Kang HM, Yang NR, Kang HG, Ha IS, etal: Outcome of Antimicrobial Therapy of Pediatric Urinary Tract Infections Caused by Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae: Infect Chemother. 2013 Dec; 45(4): 415–421.
16. Birgy A, Bidet P, Genel N, Doit C, Decre G, Bingen E: Phenotype screening of Carbapenemases and Associated beta lactamases in Carbapenam resistant Enterobacteria: Journal of Clinical Microbiology. April 2012; vol 50(4). P 1295-1302.

Source of Support: None Declared
Conflict of Interest: None Declared