Original Article

Ertapenem for Treatment of Extended-spectrum Beta-lactamase-producing and Multidrug-resistant Gram-negative Bacteraemia

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Abstract

Introduction: Imipenem and meropenem are treatment of choice for extended-spectrum beta-lactamase (ESBL)-positive gram-negative bacteraemia. They may select for carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*; ertapenem may not do so as it is inactive against these bacteria. Clinical efficacy of ertapenem in ESBL-producing gram-negative bacteraemia is limited. Materials and Methods: Retrospective study of patients with ESBL-positive gram-negative bacteraemia treated with ertapenem was undertaken. Results: Forty-seven patients with multidrug-resistant gram-negative bacteraemia (79% produced ESBL) were treated with ertapenem for a median duration of 11 days. The median age was 70 years. Septic shock occurred in 19% and mechanical ventilation was needed in 17%. *Klebsiella pneumoniae* comprised 53% and *Escherichia coli* 26%. Urinary infection accounted for 61% and hepatobiliary 15%. Favourable clinical response occurred in 96%. Attributable mortality was 4%. Conclusion: Ertapenem is promising in culture-guided step-down therapy of ESBL-positive gram-negative bacteraemia.

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Key words: Bloodstream infection, Carbapenem resistance, *Klebsiella pneumoniae*

Introduction

Extended-spectrum beta-lacatamase (ESBL)-producing gram-negative bacteraemia is optimally treated with carbapenem.[1,2] In our institution, *Escherichia coli* and *Klebsiella pneumoniae* are the most common and third most common causes of bacteraemia, and 21% of *E. coli* and 51% *K. pneumoniae* produced ESBL. There has been increasing use of imipenem and meropenem[3] to treat ESBL-producing Gram negative bacterial infections and empirically to treat severe sepsis. Consequently, carbapenem resistance in *Acinetobacter baumannii* (67%) and *Pseudomonas aeruginosa* (15%) is high and associated with carbapenem use.[4,5]

Ertapenem has in vitro activity against ESBL-producing gram-negative bacteria.[6] There are only 2 reports of its clinical efficacy in ESBL-producing gram-negative bacterial infections with few cases of bacteraemia.[3,7] We seek to evaluate its clinical efficacy in treating ESBL-producing and other multidrug-resistant gram-negative bacteraemia.

Materials and Methods

All case records of patients prescribed ertapenem between 1 November 2003 and 30 June 2006 were retrieved from our Pharmacy database. Exemption for ethics approval was obtained from our Institutional Review Board. Medical records of patients who had ESBL-producing and other multidrug-resistant (defined as being resistant to 4 or more classes of antibiotics including third-generation cephalosporins) gram-negative bacteraemia were reviewed. Demographic data, medical co-morbidities, source of bacteraemia, severity of infection, microbiological cultures, prior antibiotic treatment, duration of ertapenem, adverse drug reaction and outcome data were extracted. Bacteraemia occurring within the first 48 hours of hospitalisation is defined as community-acquired while that occurring after 48 hours of hospitalisation is defined as nosocomial. Bacteraemia is considered healthcare-associated if a patient had prior hospitalisation within the last 3 months of current admission, or is a nursing home resident.

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Table 1. Demographic and Clinical Data of Patients Receiving Ertapenem for Multidrug-resistant gram-negative Bacteraemia

Number of patients, n	47
Median age (range), y	70 (24-91)
Male gender, n (%)	30 (64)
Nursing home residence, n (%)	7 (15)
Prior hospitalisation within last 3 months, n (%)	25 (53)
Prior positive culture with same bacteria within last 3 months, n (%)	6 (13)
Co-morbidity, n (%)	
Diabetes mellitus	18 (38)
Cardiac disease	13 (28)
Cancer	11 (23)
Renal disease	8 (17)
Seizure	3 (6)
Liver disease	2 (4)
Corticosteroid therapy	2 (4)
Pulmonary disease	1 (2)
Human immunodeficiency virus	1 (2)
Source of bacteraemia, n (%)	
Urinary	29 (61)
Hepatobiliary	7 (15)
Vascular access device	6 (13)
Surgical site	3 (6)
Pneumonia	1 (2)
Skin and soft tissue	1 (2)
Severity of infection, n (%)	
Blood pressure <90/60 mmHg	9 (19)
Supplemental oxygen	13 (28)
Intensive care unit admission at onset of bacteraemia	5 (11)
Inotrope requirement	4 (9)
Mechanical ventilation	8 (17)

Table 2. Microbiology Data and Initial Antibiotic Treatment of Patients Receiving Ertapenem for Multidrug-resistant Gram-negative Bacteraemia

Aetiology of bacteraemia, n (%)	
Klebsiella pneumoniae	25 (53)
Escherichia coli	12 (26)
Proteus mirabilis	3 (6)
Klebsiella species	2 (4)
Klebsiella oxytoca	2 (4)
Enterobacter cloacae	1 (2)
Morganella morganii	1 (2)
Serratia marcescens	1 (2)
Antibiotic resistance, n (%)	
Ceftriaxone/ceftazidime	47 (100)
Amoxycillin-clavulanate	34 (72)
Piperacillin-tazobactam	20 (43)
Ciprofloxacin	36 (77)
Co-trimoxazole	38 (81)
Gentamicin	25 (53)
Amikacin	3 (6)
Courses of initial antibiotic treatment*, n (%)	
Narrow-spectrum penicillin	1 (2)
Narrow-spectrum cephalosporin	1 (2)
Amoxycillin-clavulanate	7 (15)
Piperacillin-tazobactam	4 (9)
Third-generation cephalosporin	23 (49)
Aminoglycoside	3 (6)
Fluoroquinolone	6 (13)
Imipenem	25 (53)
Meropenem	5 (11)

* Many patients were given more than one antibiotic, either sequentially or in combination, prior to starting ertapenem.

In determining the source of bacteraemia, we required compatible clinical, laboratory, microbiological and/or radiological features to support diagnoses of urinary, hepatobiliary, surgical site, skin and soft tissue, bone and joint, and vascular access device infections and pneumonia. Outcome evaluated comprised clinical response (cure defined as resolution of clinical signs and symptoms, improvement as partial resolution, and failure as no resolution), attributable death (death during treatment for current episode of infection without an alternative cause of death) and death at hospital discharge, and relapse of same bacterium either at same or another site within 3 months.

Gram-negative bacilli were identified by the Microbact gram-negative identification system (Oxoid, Basingstoke, United Kingdom). Antibiotic susceptibility was determined by disk diffusion test on Mueller-Hinton Agar according to methodology and inhibition zone diameters recommended by the Clinical and Laboratory Standards Institute. ESBL was detected by modified double-disk synergy test with cefotaxime and ceftazidime disks (Becton- Dickinson, Sparks, Maryland, USA) on opposite sides of an amoxycillin-clavulanate disk at 25 mm apart.[8]

Descriptive statistics were used to report data. Categorical variables were compared using Fisher's exact test. $P < 0.05$ was considered statistically significant.

Results

Forty-seven patients with a median age of 70 years (range, 24 to 91) were assessed. Table 1 shows detailed demographic and clinical data. Nosocomial bacteraemia defined as onset more than 48 hours after admission comprised 51%. Of the remainder apparent community-onset bacteraemia, 70% had prior hospitalisation within 3 months, and 43% of those without recent hospitalisation were nursing home residents. Hence, 91% of bacteraemia were healthcare-associated.

The 3 most common sources of bacteraemia were urinary in 61% of patients (61% associated with urinary catheterisation), hepatobiliary in 15% of patients and vascular access device-associated infections in 13% of patients. Nineteen per cent of patients had septic shock at the time of bacteraemia. Seventeen per cent of patients required mechanical ventilation.

Seventy-nine per cent of bacteraemia (37 of 47) were associated with ESBL-production, 17% (8 of 47) were apparent ESBL-negative gram-negative bacteraemia resistant to both ceftriaxone and ceftazidime, and 4% (2 of 47) were ESBL-negative gram-negative bacteria with inducible chromosomal beta-lactamase. Co-resistant phenotypes to other antibiotics tested (Table 2) between ESBL-positive and ESBL-negative third generation cephalosporin-resistant gram-negative bacteria were similar (P >0.05).

The 3 most common bacteria isolated were *K. pneumoniae* (53%), *E. coli* (26%) and *Proteus mirabilis* (6%). All episodes of bacteraemia were mono-microbial. Table 2 shows microbiology and prior antibiotic treatment data. Of antibiotic treatment prior to ertapenem, 64% had carbapenem. Of those not on carbapenem, the 3 most common antibiotics prior to ertapenem were third-generation cephalosporin (49%), amoxycillin-clavulanate (15%) and fluoroquinolone (13%).

There was median delay of 4 days (range, 0 to 18) before ertapenem was started. The median duration of ertapenem use was 11 days (range, 2 to 58). Sixty-two per cent of ertapenem use was step-down from imipenem or meropenem while 38% was from an inactive antibiotic. Median length of hospitalisation was 28 days (range, 11 to 292).

Favourable clinical response comprising cure and improvement occurred in 91% (43 of 47). Four died (9%), 2 of whom were being treated with ertapenem for a current episode of infection. Attributable mortality was 4% (2 of 47); there was no persistent bacteraemia in both cases who were on 5 days of ertapenem prior to demise. Relapse within 3 months with the same bacteria was noted in 6% (3 of 47), 2 of whom had indwelling urinary catheter. The third patient was an injecting drug user with ESBL-positive *K. pneumoniae* bacteraemia due to vascular access device. In all 3 cases, ertapenem remained active in vitro against the isolated bacteria.

Ertapenem was well tolerated with adverse drug reaction noted in 4% (2 of 47). One patient had diarrhoea, previously treated with piperacillin-tazobactam and imipenem. A second patient without prior epilepsy developed seizure after 4 days of ertapenem, previously treated with piperacillin-tazobactam. Her postoperative seizure was attributed to sepsis from a diabetic foot infection resulting in an above knee amputation.

Discussion

In our institution, *E. coli* comprised 22% and *K. pneumoniae* 12% of bacteraemia with increasing use of carbapenem to treat ESBL-producing gram-negative bacteraemia. Consequently, 67% of *A. baumannii* and 15% of *P. aeruginosa* are resistant to carbapenem.

Ertapenem has limited activity against *A. baumannii* and *P. aeruginosa.* [6] While there is concern of selection of carbapenem-resistant *P. aeruginosa* in vitro,[9] 2 reports have shown a decrease in carbapenem-resistant *P. aeruginosa.*[10,11]

The current "gold standard" treatment for ESBL-producing gram-negative bacteraemia is imipenem or meropenem.[1,2] There are 2 reports of ertapenem in treating ESBL-producing gram-negative bacterial infections, 1 in ventilator-associated pneumonia with 3 episodes of bacteraemia[7] and another mainly in urinary infections with 13 episodes of bacteraemia.[3] Our current report provides further evidence that ertapenem may be effective in 47 episodes of multidrug-resistant gram-negative bacteraemia, 79% of which were ESBL-producing. Ertapenem was the only effective antibiotic in 38% of cases.

The 91% favourable clinical response, 8% overall and 4% attributable mortality in our study compared favourably with 3.7% mortality in ESBL-positive *K. pneumoniae* bacteraemia treated with imipenem (n = 27),[1] 12.9% mortality in ESBL-positive *E. coli* or *K. pneumoniae* bacteraemia treated with carbapenem (n = 62),[12] 80% clinical response in ESBL-positive *K. pneumoniae* bacteraemia treated with imipenem (n = 10),[2] and 26% mortality in ESBL-positive *Enterobacter aerogenes* infection (22% bacteraemia) treated with either imipenem or meropenem (n = 22).[13]

Limitations of our study include retrospective design, potential selection bias, median delay of 4 days in starting ertapenem and small numbers (albeit comparable to studies on imipenem or meropenem for ESBL-producing gram-negative bacteraemia). Further study of immediate step-down therapy on obtaining antibiotic susceptibility results should be done.

In conclusion, ertapenem is promising in culture-guided step-down treatment of ESBL-producing gram-negative bacteraemia. It may be preferred to imipenem or meropenem because of lower cost,[3] feasibility in outpatient parenteral antibiotic therapy[14] and potential benefit in reducing carbapenem resistance in *A. baumannii* and *P. aeruginosa.*[10,11]

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