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Original Article

A randomized controlled trial of sitafloxacin vs. ertapenem as a switch therapy after treatment for acute pyelonephritis caused by extended-spectrum β-lactamase-producing *Escherichia coli*: A pilot study☆

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ABSTRACT

Background: The overuse and misuse of carbapenems have contributed to the antibiotic resistance crisis. The role of oral fluoroquinolones as a switch therapy for the treatment of urinary tract infection from *Escherichia coli* (ESBL-EC) is limited.
Objective: To compare the clinical and bacteriological efficacy of sitafloxacin and ertapenem for non-bacteremic acute pyelonephritis caused by ESBL-EC.
Methods: A prospective randomized controlled trial of patients with acute pyelonephritis caused by ESBL-EC was performed as a pilot study. One of the carbapenems was initially given to the patients. After day 3, patients were randomized to receive either sitafloxacin or ertapenem.
Results: Thirty-six patients were enrolled: 19 (52.8%) in the sitafloxacin group and 17 (47.2%) in the ertapenem group. There was no statistically significant difference in baseline characteristics between the two groups except a lower proportion of previous urinary catheter insertion in the sitafloxacin group (15.8% vs. 52.9%, $p = 0.018$). Signs and symptoms at presentation were similar between the two groups except a higher proportion of patients with chills in the sitafloxacin group (68.4% vs. 29.4%, $p = 0.019$). At day 10, all but one patient in the ertapenem group had clinical cure. Microbiological eradication was comparable between the sitafloxacin and ertapenem groups (84.2% vs. 75%, $p = 0.677$). There were no significant adverse effects.
Conclusions: Treatment of non-bacteremic acute pyelonephritis caused by ESBL-EC with carbapenem followed by oral sitafloxacin is effective and well-tolerated. Sitafloxacin may be considered as an alternative choice of switch therapy in this clinical setting.

1. Introduction

As many as 80% of urinary tract infections (UTIs) are caused by *Escherichia coli* [1,2]. Since the first clinical isolation in 1983, extended-spectrum β-lactamase (ESBL)-producing organisms have become recognized as a worldwide problem, and their incidence has been increasing [3,4]. ESBLs, which are found predominantly in *Klebsiella pneumoniae* and *E. coli*, can hydrolyze all penicillins, cephalosporins, and monobactams [5], but they do not affect carbapenems (e.g. imipenem or meropenem). Cephamycins (e.g. cefoxitin and cefotetan) are not hydrolyzed by majority of ESBLs, but they are hydrolyzed by associated AmpC-type β-lactamase. ESBL-producing *E. coli* (ESBL-EC) are now a frequent cause of infection in the community and in healthcare centers [6–8]. In recent years, an increase in infection with such ESBL-producing organisms has been observed in outpatient settings, especially

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related to UTIs, and treatment options have been reduced to a limited number of antibiotics [9–11].

Treatment of infection with ESBL-EC is difficult because the organisms are frequently resistant to multiple antibiotics. Carbapenems, which are not affected by ESBLs, are considered the drugs of choice for treating severe infections caused by ESBL-producing organisms. *In vitro*, ESBL-producing organisms may sometimes appear to be susceptible to β-lactams/β-lactamase inhibitors, third- and fourth-generation cephalosporins, aminoglycosides, and fluoroquinolones. Susceptibility rates for these antibiotics are 0–80%, depending on the geographical location of the study site [12,13]. Clinicians are increasingly considering using carbapenems either as empiric or definitive therapy in moderate or severe community-onset and nosocomial infections whenever an ESBL-producing organism is suspected or demonstrated. This may be leading to an increase in the consumption of carbapenems, which is particularly worrisome in a scenario where carbapenemase-producing organisms are also spreading [14,15]. In addition, widespread use of carbapenems may be associated with further selection of pathogens with acquired (*K. pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*) and inherited (*Stenotrophomonas maltophilia*) antibiotic resistance [16,17]. Thus, alternatives to carbapenems for the treatment of ESBL-producing organism infections are urgently needed.

Fluoroquinolones may be considered as the treatment of choice for UTIs due to ESBL-producing organisms if there is no *in vitro* resistance to fluoroquinolones [18]. Unfortunately, increasing *in vitro* resistance of ESBL-producing organisms to fluoroquinolones could limit the role of these antibiotics in the future [6]. Sitafloxacin, a broad-spectrum oral fluoroquinolone, is active against many gram-positive, gram-negative, and anaerobic bacteria, including strains resistant to other fluoroquinolones [19]. It was approved in Japan for the treatment of respiratory tract infection and genitourinary tract infection. Several *in vitro* activity studies regarding sitafloxacin have been conducted showing that sitafloxacin is very active against a variety of bacteria, including *Streptococcus pneumoniae*, *Staphylococcus aureus*, Enterobacteriaceae, *P. aeruginosa*, *A. baumannii*, and *Bacteroides fragilis* [20–24]. Furthermore, a recent *in vitro* activity study found that sitafloxacin is more active than levofloxacin, ciprofloxacin, and moxifloxacin against bacteria isolated from patients with UTIs, including antibiotic-resistant bacteria such as ESBL-producing gram-negatives, and carbapenem-resistant *A. baumannii* [25].

The aim of our study was to evaluate sitafloxacin as compared to ertapenem as a switch therapy for the treatment of non-bacteremic acute pyelonephritis caused by ESBL-EC. Clinical and bacteriological outcomes of participants were evaluated. We hypothesized that if sitafloxacin could be successfully applied in this clinical setting, the lower rate of carbapenem use might reduce multi-drug resistant organism problems.

2. Materials and methods

2.1. Study design

A prospective, open-label, randomized, controlled trial was conducted at Ramathibodi Hospital, a 1200-bed university hospital in Bangkok, Thailand, from November 2012 to June 2015. Written informed consent was obtained from all patients. The protocol was approved by the institutional review board of the Faculty of Medicine Ramathibodi Hospital, Mahidol University. This study was registered at ClinicalTrials.gov under registration number NCT02537847.

When the results of urine culture were reported, the patients were then allocated to oral sitafloxacin treatment or intravenous (IV) ertapenem treatment in a 1:1 ratio. After randomization, all patients were initially given one of the IV carbapenems for 3 days and then switched to oral sitafloxacin or IV ertapenem. Carbapenems included meropenem 1 gm IV every 8 h, imipenem 500 mg IV every 6 h, doripenem 500 mg IV every 8 h, and ertapenem 1 gm IV once daily. Randomization was performed using a computer-generated random number allocation schedule with a block size of four. The patients were allocated to the sitafloxacin group or the ertapenem group determining by the sealed envelope method. The total duration of antibiotic treatment was 10 days.

2.2. Patients

Both hospitalized and non-hospitalized patients were considered eligible if they: (1) were over 18 years of age; (2) had a presumptive diagnosis of acute pyelonephritis, defined as pyuria (≥10 leukocytes per high-power field (HPF) in urine analysis) combined with all of the following: fever (body temperature ≥ 38 °C), urinary syndrome (dysuria, urgency, or urinary frequency), flank pain, or costovertebral angle tenderness; (3) had positive urine culture of $\geq 10^5$ colony-forming units (CFU)/mL ESBL-EC; and (4) voluntarily consented to be enrolled in the study. Exclusion criteria were as follows: (1) urine culture growing more than one organism; (2) severe sepsis or septic shock; (3) positive hemoculture; (4) had other sources of infection; (5) known mechanical abnormality of the urinary tract; (6) immunocompromised host, e.g. receiving prednisolone >15 mg/day, post-organ transplantation, aplastic anemia, or solid and hematologic malignancy receiving chemotherapy; (7) retaining Foley catheter; (8) pregnancy or lactation; (9) previous UTIs within four weeks; and (10) contraindication to fluoroquinolones and/or carbapenems.

All eligible patients were given one of the carbapenems as an initial antibiotic agent. After day 3, patient were enrolled and randomized to either the sitafloxacin or ertapenem group. All antibiotics were renally adjusted according to creatinine clearance (CrCl), as calculated by the Cockcroft–Gault equation. For patients receiving sitafloxacin, the dosage for those with CrCl more than 50 mL/min was 100 mg twice daily. Among patients with renal impairment, the dosage was 50 mg once daily for patients with CrCl 30–50 mL/min and 50 mg every 48 h for those with CrCl 10–30 mL/min. Patients who were allocated to the ertapenem group were given ertapenem 1 g infused over 30 min once daily; the dosage was 0.5 g once daily for patients with CrCl <30 mL/min.

On the day of enrollment, initial laboratory evaluation included complete blood count (CBC), hemoculture, serum creatinine (Cr), alanine aminotransferase (ALT), urinalysis (UA), and urine culture (UC). The follow-up laboratory monitoring at day 3 and day 10 included CBC, hemoculture, ALT (day 10 only), UA, and UC. On day 7, clinical assessment of treatment outcomes, both symptoms and drug tolerability, was performed by interviewing the patients at the ward or via telephone if the patient had been discharged. Adherence to medication was checked by pill-counting and medical records. The tolerability of study drugs and occurrence of adverse events (AEs) were evaluated by a physician. At the last follow-up visit on day 30, UA and UC were reassessed. The patients were evaluated for clinical signs and symptoms of acute pyelonephritis at the clinic on day 10 and day 30. During the study period, based on clinical judgment the physician could terminate the treatment for safety reasons or due to abnormal laboratory findings attributed to sitafloxacin or ertapenem administration.

2.3. Study outcomes

The clinical responses were based on clinical signs and symptoms of acute pyelonephritis as determined by physical