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Comparative study of ceftibuten and cefixime in the treatment of complicated urinary tract infections

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Between August 1996 and May 1998, a total of 62 patients who had complicated urinary tract infections treated at the Taipei Veterans General Hospital were enrolled into this study. This prospective, randomized, open-labeled trial aimed at comparing the efficacy and safety of ceftibuten and cefixime, prescribed each at a dose of 200 mg twice daily, in treating complicated urinary tract infection. Seventeen patients were later excluded from the analysis because of resistant pathogens (7 patients), uncomplicated urinary tract infection (6), initial culture negative for bacteria (3), and infective endocarditis (1). The remaining 45 patients were categorized into ceftibuten (n = 23; mean age, 71.3 years) and cefixime (n = 22; mean age, 62.8 years) treatment groups. No significant difference in demographic data and clinical characteristics was found between the 2 groups. The clinical efficacy rate (78.3% vs 77.3%, p=0.9) and bacteriological eradication rate (52.2% vs 63.6%, p=0.08) were similar between the ceftibuten and the cefixime group. Adverse effects caused by ceftibuten treatment included diarrhea and slight elevation of the serum level of liver transaminase in 2 (6.5%) patients. Those caused by cefixime treatment included slight elevation of serum level of liver transaminase in 2 (6.5%) patients and skin rash in 1 (3.2%) patient. All of these adverse effects resolved quickly after the regimen had been completed, and no patient discontinued the regimen because of the adverse effects. The results suggest that oral administration of ceftibuten 200 mg twice daily is as effective and safe as oral administration of cefixime 200 mg twice daily in the treatment of complicated urinary tract infections.

Key words: Cefixime, ceftibuten, complicated urinary tract infection

Urinary tract infection (UTI) is a common clinical problem. Although oral penicillin and cephalosporins have been important treatments of UTI, the emergence of β-lactamase-mediated resistance had now limited their usefulness [1]. Complicated UTI is often caused by more resistant microorganisms [2], and empirical therapy with conventional oral antibiotics may result in a limited effectiveness in treating UTI at outpatient clinics.

Ceftibuten is an orally active third-generation cephalosporin with bactericidal activity against a wide range of pathogens, which included the majority of gram-negative pathogens and certain gram-positive pathogens [3,4]. Cefixime, the first orally administered third-generation cephalosporin approved in Taiwan, has been found to have high efficacy and safety in treating complicated and uncomplicated UTI [5]. This study aimed to compare the clinical and microbiological efficacy of ceftibuten and cefixime in the treatment of complicated UTI.

Materials and Methods

From August 1996 through May 1998, a prospective, randomized, open-labeled comparative study of ceftibuten and cefixime in the treatment of complicated UTI was conducted in the Taipei Veterans General Hospital. Both outpatient and hospitalized patients were considered eligible, if they were above 18 years of age and had complicated UTI caused by gram-negative bacterium that was susceptible to the tested drug. Urinary tract infection was defined as more than 10^5 colony-forming unit (CFU)/mL of urine before treatment and pyuria with more than 5 white blood cells under high power field before antibiotics treatment. Patients who had defects or predisposing factors to UTI such as congenital abnormality, distortion or obstruction of the urinary tract, formation of stones in the urinary tract, placement of an indwelling catheter, prostatic hypertrophy, or neurological deficits interfering with

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the normal flow of urine and urinary defense, and thereafter developed UTI were considered as having complicated UTI [6]. Patients were excluded from the study if they: (1) were unable to accept non-parenteral treatment; (2) had previous anaphylactic reaction to any antibiotics, or known hypersensitivity to penicillins or cephalosporins; (3) had severe impairment of liver function, defined as a serum level of transaminase greater than 3 times the upper limit, or severe renal dysfunction, defined as a serum level of creatinine above 2 mg/dL; (4) were lactating or pregnant; (5) were infected with ceftibuten- or cefixime-resistant organisms; (6) had an improved condition under other empirical therapy; and (7) had a serious disease such as malignancy, which could potentially shorten the life-span during the study period. Written informed consent for participation was obtained from all patients or their families, after the effect and possible side-effects of the tested drugs were clearly explained.

Two 100-mg ceftibuten capsules were given to the study group every 12 h, and 2 capsules of 100-mg cefixime were given in the control group every 12 h. The regular treatment course was completed in 10 days, but could be extended to 14 days depending on the clinical condition of the patient.

The clinical features compared between 2 groups included demographic characteristics, medical history, drug history, physical examinations, laboratory data, and culture of blood and urine at the time of enrollment. Body temperature was recorded during the study period. Symptoms related to UTI included dysuria, frequency, and urgency, and other symptoms were also recorded. Urine specimens for urinalysis and culture were collected using clean-catch or catheterization method on day 1, 4, 10, the last day of the treatment, and 2 weeks after completion of the treatment. Blood samples for biochemical tests of renal and liver function were collected on day 1, 4, and 10, and on the last day of treatment if it exceeded 10 days. Blood culture was performed on day 1 of treatment.

Clinical efficacy was evaluated 3 days after treatment. Patients were followed-up 2 weeks after completion of treatment for symptoms and signs. The efficacy of treatment was categorized into the following 4 groups: (1) cure–all symptoms and signs disappeared and no relapse occurred within 2 weeks after the completion of treatment; (2) improvement–improvement of all signs and symptoms; (3) failure–persistence or worsening of the symptoms and signs; and (4) relapse–reappearance of symptoms and signs of the original infection at the end of therapy or within 2 weeks after completion of treatment. Bacteriological responses to the treatment were classified as the followings: (1) eradication–bacterial isolates identified before treatment were not isolated in follow-up cultures; (2) persistence–bacterial isolates identified before treatment were found in follow-up cultures; (3) superinfection–new bacterial isolates that were either susceptible or resistant to the study drug; and (4) eradication with relapse–the disappeared original isolate recurred in culture of the specimen collected 2 weeks after the completion of the treatment.

According to the severity of the adverse effects during the period of study, physicians may choose to terminate the treatment based on a clinical judgment about the safety of treatment. The time and severity of clinical symptoms and signs were recorded and analyzed to determine their relationship with treatment.

Categorical variables between the 2 groups were compared using the chi-square or the Fisher's exact test for qualitative data, and Student t test was used to analysis the quantitative data. When applicable, tests were 2-tailed. A p value lower than 0.05 was considered significant.

Results

Sixty-two patients were enrolled in this study, and each treatment group comprised of 31 patients. Seventeen patients (8 ceftibuten, 9 cefixime) were excluded because of resistant pathogen (7patients), uncomplicated UTI (6), initial culture negative for bacteria (3), or infective endocarditis (1). Data from the remaining 45 patients (23 ceftibuten, 22 cefixime) were included in the analysis.

Table 1. Demographic characteristics, daily dose, and duration of treatment of patients receiving ceftibuten or cefixime in complicated UTI remedy

	Ceftibuten (n = 23)	Cefixime (n = 22)
Age (yr), Mean ± SD (range)	71.3 ±10.5 (46-87)	62.8 ± 18.1(24-85)
Male:Female	12:11	11:11
Daily dose	200 mg q12h	200 mg q12h
Days of treatment, mean ± SD (range)	10.1 ± 2.2 (4-14)	10.5 ± 2.0 (5-14)

Abbreviation: UTI = urinary tract infection

Table 2. Complicating factors in patients receiving ceftibuten or cefixime for the treatment of complicated UTI

Complicating factor	Ceftibuten (n = 23)	Cefixime (n = 22)
Benign prostate hypertrophy	11	5
Calculi	7	10
Indwelling urinary catheterization	5	3
Neurogenic bladder	5	6
Renal cyst	5	4
Urologic procedure (diagnostic/surgical)	3	1
Other structural abnormality	3	8
Chronic cystitis	2	4

No significant difference was found in the demographic data, daily dosage, and average duration of treatment between the 2 groups of treatment (Table 1). Diseases that predisposed patients to develop complicated UTI are listed in Table 2. The bacterial isolates, bacteriological responses to treatment, and clinical efficacy of antibiotic treatment in both groups of patients are shown in Tables 3 and 4. *Escherichia coli* was the most common pathogen in both groups, followed by *Proteus mirabilis* and *Klebsiella pneumoniae* (Table 3).

The clinical efficacy of antibiotic treatment was evaluated according to the daily responses of presenting symptoms and signs. In the ceftibuten group, 12 (52.2%) patients were cured, 6 (26.1%) showed improvement, 1 (4.3%) had treatment failure, and 4 (17.4%) had relapses. In the cefixime group, 12 (54.6%) patients were cured, 5 (22.7%) showed improvement, 2 (9.1%) had failure, and 3 (13.6%) had relapses. The results indicate that the clinical efficacy of ceftibuten in the treatment of complicated UTI was similar to that of cefixime (78.3% vs 77.3%, p=0.9).

In the ceftibuten treatment group, the pathogens were eradicated in 12 (52.2%) patients (Table 4). One patient had persistent infection caused by *K. pneumoniae*; 1 had superinfection caused by glucose-nonfermentative gram-negative bacillus; and 9 (39.1%) had relapses, 8 of whom were infected by *E. coli* and 1 by *P. mirabilis*. In the cefixime group, the pathogens were eradicated in 14 (63.6%) patients; 3 (13.6%) patients had relapse, 2 of whom was infected by *E. coli* and 1 by *P. mirabilis*; and 5 (22.7%) patients had superinfection, 1 of them was infected by *Citrobacter freundii*, 1 by *Morganella morganii*, 1 by *Enterococcus*, 1 by *Pseudomonas aeruginosa*, and 1 by *E. coli* and glucose-nonfermentative gram-negative bacillus.

The adverse effects in the ceftibuten group included diarrhea in 1 patient and slight elevation of serum level of transaminase in another; in the cefixime group, adverse effects included skin rash in 1 patient and slight elevation of liver transaminase in 2. All of these patients completed the regimens despite the adverse effects, and their symptoms and signs from the adverse effects resolved after the treatment was completed.

Table 3. Causative pathogens in patients receiving ceftibuten or cefixime for the treatment of complicated UTI

Pathogen	Ceftibuten[a] n = 23 (%)	Cefixime[a] n = 22 (%)
Escherichia coli	20 (87.0)	18 (81.8)
Proteus mirabilis	2 (8.7)	3 (13.6)
Klebsiella pneumoniae	1 (4.3)	1 (4.6)

[a] p = 0.87.

Discussion

Ceftibuten is a third-generation cephalosporin that is orally administered. The major pharmacokinetic characteristics of ceftibuten are as follows: (1) oral bioavailability of 70% to 90%; (2) half-life of 2.23 ± 0.89 h; and (3) excretion of 67.5% to 75.2% of an unchanged form of drug in urine 24 h after administration [4]. Ceftibuten also possesses excellent bactericidal activity against gram-negative and certain gram-positive pathogens, but has weaker antibacterial activity to *P. aeruginosa* and anaerobes [3,4,7-12]. Most strains of *Enterobacteriaceae*, which included *E. coli*, *Citrobacter diversus*, *K. pneumoniae*, *Klebsiella oxytoca*, *P. mirabilis*, *P. vulgaris*, *Providencia rettgeri*, *Providencia stuartii*, *Salmonella* spp., *Shigella* spp., and *Yersinia enterolitica* are susceptible to ceftibuten [3,4]. *M. morganii* and *Serratia marcescens* are moderately susceptible, whereas the majority strains of *C. freundii*, *Enterobacter aerogenes*, and *Enterobacter cloacae* were

Table 4. Bacteriological and clinical responses of patients receiving ceftibuten or cefixime for the treatment of complicated UTI

	Ceftibuten n = 23 (%)	Cefixime n = 22 (%)
Bacteriological response[a]		
Eradication	12 (52.2)	14 (63.6)
Relapse	9 (39.1)	3 (13.7)
Superinfection	1 (4.3)	5 (22.7)
Persistent	1 (4.3)	0
Clinical response[b]		
Cure	12 (52.2)	12 (54.6)
Improvement	6 (26.1)	5 (22.7)
Failure	1 (4.3)	2 (9.1)
Relapse	4 (17.4)	3 (13.6)

[a] p=0.08.
[b] p=0.9.

resistant to ceftibuten [3,4]. The activity of ceftibuten was shown to be greater than that of cefaclor and cefuroxime, and is comparable with that of cefixime against *Enterobacteriaceae* [4]. In a study of comparative susceptibility of clinical isolates producing β-lactamase, however, 73% of the tested isolates were susceptible to ceftibuten versus 22% to cefixime in large inocula [13]. It has also been reported that ceftibuten is more potent than cefixime against most *Enterobacteriaceae* [14,15]. Because ceftibuten is well absorbed, its impact on the normal flora in the intestine is reduced.

Studies of clinical effectiveness have shown that ceftibuten had an efficacy rate of 65% to 83% in treating complicated UTI when it was taken once or twice daily (400 mg/d) [4]. The efficacy rate of ceftibuten can reach 93% to 100% in the treatment of uncomplicated UTI [4,16], and 90% in the treatment of infants and children with complicated or recurrent UTI [4].

In this study, the clinical efficacy rate in the treatment of complicated UTI in ceftibuten group patients (78.3%) was not significantly different from that in the cefixime group (77.3%). The bacteriological eradication rate for ceftibuten was also not different from cefixime (52.2% vs 63.6%; p=0.08) in the treatment of complicated UTI. The eradication rate of ceftibuten for complicated UTI in this study (52.2%) was similar to the reported rate, which ranges from 40% to 80% [4,17,18]. The percentage of relapse after receiving ceftibuten treatment (39.1%) was higher than that of cefixime treatment (13.7%). Frequent relapses of infections mean inadequacy in treatment duration. A possible explanation for the different relapse rate may be the differences in predisposing diseases. For example, benign prostate hypertrophy might be complicated with prostatitis, and renal cyst might be infected (Table 2). When patients with relapse and superinfection were considered, no statistical significance in bacteriological failure was noted between the 2 treatment groups (43.4% vs 36.4%, p>0.05). Because of the use of different inclusion and exclusion criteria, differences in the prevalence of pathogens, and variations in treatment regimens, it is difficult to compare the relapse rate in treating complicated UTI between this study and other studies. In the study of Gleckman *et al* [19], *in vitro* susceptible drug was used in treating complicated UTI, but a high relapse rate (52%) was also noted; of the patients who had completed the 2-week course of therapy, sterility of the urine for a minimum of 6 weeks after therapy was noted in 29%. These patients had many predisposing lesions that might have caused the high relapse rates. Results of this study suggest that correcting the reversible predisposing factors and a longer antibiotic treatment period may be essential in increasing the clinical efficacy of antibiotic treatment and preventing relapse in complicated UTI.

Ceftibuten had been shown to be safe in studies from many well-developed countries [3,4,20-23]. The adverse reactions to ceftibuten found in this study were similar to those of other oral β-lactam antibiotics [3]. Thus, ceftibuten treatment appears to offer a high level of safety.

The failure of patients to comply with antibiotic regimens has an extensive impact on the cost and strategies of medical care. It has been shown that compliance is about 30% on a 4-time daily regimen, which would be improved to 40% to 84% if the regimen is reduced to 3 times daily, to 50% to 93% on a twice-daily regimen, and to 93% to 96% on a once-daily regimen [24-27]. In this study, the twice-daily regimen of ceftibuten may have contributed to the improved therapeutic compliance compared with a 4-time daily regimen in the treatment of complicated UTI [24].

In conclusion, this study has demonstrated that ceftibuten had similar efficacy and safety to cefixime in the treatment of complicated UTI.

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