COMPARISON OF THE EFFICACY OF CEFTIBUTEN AND NORFLOXACIN IN THE TREATMENT OF ACUTE GASTROINTESTINAL INFECTION IN CHILDREN

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Abstract. A prospective randomized study was conducted at an infectious disease hospital in Thailand. Ceftibuten was compared with norfloxacin, both given orally for five days for treatment of acute gastroenteritis in children. One hundred and seventy cases were included in the study. Eighty-eight cases were treated with ceftibuten and eighty-two cases with norfloxacin. The baseline characteristics of the patients in both treatment groups were similar. The results showed that mean durations of diarrhea in the ceftibuten and norfloxacin groups were 2.48 days and 2.29 days, respectively, but there was no statistically significant difference between the two groups ($p > 0.05$). There were *Salmonella* spp and *Shigella* spp isolated in both treatment groups and all were susceptible to both antibiotics. The mean durations of *Salmonella* diarrhea in the ceftibuten and norfloxacin groups were 2.7 and 2.2 days, respectively, while those of *Shigella* diarrhea were 2.3 days and 2.0 days, respectively. There were no statistically significant differences in either comparison ($p > 0.05$). Neither complications nor clinical relapses were observed after both antibiotics' treatment.

In conclusion, ceftibuten is as good as norfloxacin in treating gastrointestinal infection caused by *Salmonella* and *Shigella* in children. Ceftibuten is safe in children whereas norfloxacin is still controversial. The authors suggest that ceftibuten may be used as a single drug or oral step down therapy in treating community-acquired respiratory tract infections with invasive gastrointestinal infection in both healthy and immuno-compromised children.

INTRODUCTION

Acute gastrointestinal infection remains a common disease in children, especially in the developing countries (Sirivichayakul and Thisyakorn, 1998). Its main etiologic agent is the Enterobacteriaceae group, including *Salmonella*, *Shigella*, and *Campylobacter* (Caeiro *et al*, 1999). Diarrhea is the most common presentation and occurs both in healthy and immuno- compromised children. Antimicrobial therapy is recommended for most intestinal infections because it eliminates the organisms from the feces and shortens the duration of diarrhea and other symptoms (Moolasart, 1998). Widespread use of antibiotics has resulted in the development of drug-resistant bacteria. Ampicillin and cotrimoxazole were formerly used in treatment of shigellosis and salmonellosis but treatment failures as well as high resistance rates were reported for both drugs in previous studies (Maiorini *et al*, 1993; Moolasart *et al*, 1997; Moolasart and Eampokalap, 1994).

Norfloxacin, a quinolone, is the preferred drug in treating *Salmonella* and *Shigella* diarrhea in both healthy and AIDS children since such diarrhea has developed resistance to other drugs. The use of norfloxacin in children is still controversial because its side-effects in humans are unclear (Stahlmann, 1990) even though some recent studies in England and Canada showed the safety of the new quinolone including norfloxacin in children (Wilton *et al*, 1996; Berkovitch *et al*, 1994).

Ceftibuten is a new, effective third-generation cephalosporin that has a broad spectrum of activity against most gram-negative and some gram-positive organisms (Jones and Barry, 1988). It is stable in the presence of most beta-lactamases (Owens *et al*, 1997; Helwig, 1997; Guay, 1997), rapidly absorbed after oral administration with a half-life of 2.5 hours. The minimum inhibitory concentration (MIC) of ceftibuten determined with standard inocula was lower than those of several other antibiotics (Medeiros and Crellin, 1997). It is an alternative to other antimicrobial agents with a convenient once-daily dosage in the treatment of upper and lower respiratory tract infections and twice daily (bid) in gastrointestinal infection (Jones, 1993). Previous

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study showed that organisms among the Enterobacteriaceae with plasmid-mediated resistance were most susceptible to ceftibuten < 0.5 μg/ml (Jones, 1993). The drug is also well tolerated (Barr *et al*, 1993).

The purpose of this study was to compare the the efficacy of ceftibuten and norfloxacin in the treatment of acute gastrointestinal infection in children, especially that caused by *Salmonella* and *Shigella*.

MATERIALS AND METHODS

Study design

The study was conducted among children with acute gastrointestinal infection at the Diarrhea Center of Bamrasnaradura Infectious Disease Hospital, Nonthaburi, Thailand, from 1997 to 1998. The children under the study were those aged 6 months to 12 years with acute gastroenteritis as indicated by diarrhea and fever, abdominal pain, or vomiting. Diarrhea was defined as an illness with at least three loose stools or one bloody stool in a 24-hour period. All of the patients had their history recorded and stool specimens sent for examination and culture.

Each of the patients was assigned at random to receive treatment with either ceftibuten, 9 mg/kg/day bid, or norfloxacin, 15 mg/kg/day bid, for five days. Both drugs were given orally before the results of the pretreatment stool culture were known. Dehydration and other symptoms of different degrees were treated as appropriate. The patients were followed up for two days after the end of therapy. Clinical signs, symptoms, stool appearance and adverse drug reactions were recorded.

This study was approved by the National Research Council of Thailand. The informed consent was obtained from the parents of the children who served as subjects.

Laboratory data

All stool specimens were examined for leukocytes, red blood cells and parasites, and cultured for enteropathogenic organisms before treatment and again two days post-treatment. The Enterobacteriaceae were identified by the standard biochemical test (Kelly, 1985). Antibiotic sensitivity testing was performed by the agar disk diffusion method (National Committee for Clinical Laboratory Standards, 1997).

Statistical methods.

Z-test and Student's *t*-test were used for testing the significance of differences between the means of each comparison.

RESULTS

Of the 360 patients enrolled in the trial, 170 were included in the efficacy analysis (ceftibuten, 88; norfloxacin, 82). One hundred and ninety cases (52.8%) were excluded from the study because of lost follow-up.

The patients in both treatment groups were similar in their characteristics and clinical features (Table 1). The mean ages were 1.99 years (range, 6/12 to 12 years) in the ceftibuten group and 2.18 years (range, 6/12 to 12 years) in the norfloxacin group. There was no significant age difference between both groups. All of the patients had no signs of dehydration. The pathogenic organisms isolated in both groups were *Salmonella* spp, *Shigella* spp, *Campylobacter*, and *Vibrio parahemolyticus* (Table 2). Most *Salmonella* and *Shigella* isolates were resistant to ampicillin, cotrimoxazole and tetracycline (Table 3). However, all invasive agents (*Shigella*, *Salmonella*, and *Campylobacter*) isolated were susceptible to both ceftibuten and norfloxacin. All isolated agents were eliminated on day two post-treatment in both groups.

The results of treatment are shown in Table 4. Clinical successes in the treatment of acute gastrointestinal infection in children with ceftibuten and norfloxacin were achieved in 2.48 days (range, 1 to 7 days) and 2.29 days (range, 1 to 6 days), respectively. There was no significant difference in clinical efficacy between the two groups ($p>0.05$).

The clinical successes in the treatment of acute gastrointestinal infection caused by *Salmonella* and *Shigella* are shown in Table 5. The clinical successes in treating with ceftibuten and norfloxacin of *Salmonella* infection occurred in 2.7 days and 2.2 days, respectively, while those of *Shigella* infection in 2.3 days and 2.0 days, respectively. There were no significant differences in clinical efficacy between the two treatment groups of *Salmonella* and *Shigella* gastroenteritis ($p>0.05$). Ceftibuten and norfloxacin were similar in their efficacy in relieving symptoms and signs other than diarrhea in this study.

Ceftibuten suspension was well accepted by about 80% of the patients, compared with only 20% for norfloxacin tablet (based on patient's reactions observed by their parents). Neither complications

Table 1
Characteristics and illness features of patients with acute gastrointestinal infection in the ceftibuten and norfloxacin treatment groups.

	Ceftibuten	Norfloxacin	p-value
Cases studied	88	82	
Age - average, years	1.99	2.18	>0.05
- range, years	6/12-12	6/12-12	
Sex M : F	57 : 31	49 : 33	
Clinical features			
- Fever	52	46	
- Vomiting	35	36	
- Abdominal pain	14	17	
Stool appearance			
- Watery	6	6	
- Loose	68	57	
- Mucous	22	20	
- Bloody/mucous-bloody	6	5	
Frequency of stool passing			
<10 / day	67	68	
>10 / day	21	14	
Stool examination			
+ve wbc	8	8	
+ve rbc	8	8	
+ve parasite	0	0	
Stool culture			
+ve enteropathogen	20	22	

Table 2
Stool samples with pathogenic organisms isolated before treatment in both study groups.

Pathogen	Ceftibuten N = 20	Norfloxacin N = 22
Salmonella	7	5
Shigella	4	4
Campylobacter	3	7
Aeromonas hydrophila	3	3
Others	8	7
+ve for 2 pathogens	3	2
+ve for 3 pathogens	1	1

Table 3
Clinical success of therapy for acute diarrheal cases.

	Ceftibuten N = 88	Norfloxacin N = 82	p-value
Duration in days	2.48	2.29	>0.05
Range in days	1-7	1-6	

nor relapses of disease after treatment were observed in both treatment groups. And there were no deaths in this study.

DISCUSSION

Acute gastrointestinal infection is an important cause of diarrhea and remains a major cause of morbidity and mortality in children. Antibiotic therapy has been shown to shorten the duration of diarrhea and the period of excretion. Such therapy is recommended for both *Shigella* and *Salmonella* gastroenteritis in young infants and immunocompromised patients, who are at increased risk of bacteremia. Recurrent *Salmonella* bacteremia is an AIDS-related illness (Levine *et al*, 1991).

Widespread use of antibiotics has resulted in the emergence of drug-resistant bacteria. Ampicillin and cotrimoxazole have been the drugs of choice for treating shigellosis and salmonellosis in children (World Health Organization, 1990; Richards *et al*, 1993) but the pathogens of both infections are resistant to these drugs in many parts of the world

including Thailand (Moolasart *et al*, 1997; Moolasart and Eampokalap, 1994). Nalidixic acid has been an alternative drug in treating invasive gastroenteritis with such pathogens, as recommended by WHO (World Health Organization, 1990; Richards *et al*, 1993) but there has been a rapid increase in resistance among these pathogens. *Shigella* and *Salmonella* isolates in this study were resistant to nalidixic acid in 12.5% and 41.7% of the cases, respectively. Compared with the results of previous studies conducted in the same hospital in 1994 and 1997, *Shigella flexneri* and *Salmonella* group B resistant to nalidixic acid were then found in only 3.1% (Moolasart and Eampokalap, 1994) and 10.3% (Moolasart *et al*, 1997) of the patients, respectively. It has been reported that ampicillin plus sulbactam may be an alternative regimen in the treatment of infection with multiple-drug-resistant *Shigella* strains (Ling *et al*, 1988). But there was a high resistance to such a drug combination *in vitro* in the same hospital (Moolasart and Eampokalap, 1994). A previous study showed the use of cephalosporins for treatment of shigellosis, but they were mostly ineffective (Kabir *et al*, 1986). However, a 5-day course of ceftriaxone was found successful in treating shigellosis (Varsano *et al*, 1991).

Table 4
Drug resistance patterns of *Salmonella* and *Shigella* isolates.

Drug	*Salmonella* N=12	*Shigella* N=8
Ampicillin	2 (16.7%)	2 (25%)
Colistin	0 (0%)	0 (0%)
Cotrimoxazole	6 (50%)	6 (75%)
Gentamicin	0 (0%)	0 (0%)
Nalidixic acid	5 (41.7%)	1 (12.5%)
Nitrofurantoin	3 (25%)	0 (0%)
Tetracycline	6 (50%)	6 (75%)
Norfloxacin	0 (0%)	0 (0%)
Ceftibuten	0 (0%)	0 (0%)

Norfloxacin, a quinolone, has been shown to be effective in treatment of shigellosis and salmonellosis, similar to this study. The drug has been used in treating *Salmonella* and *Shigella* diarrheal diseases in the developing countries since such infections have developed resistance to other drugs, although it has not been approved for use in children. In addition, its taste is not good and preparation inconvenient for use in children as it has no oral suspension formula.

Ceftibuten, a new oral cephalosporin, has shown its clinical potential as a drug for community-acquired respiratory tract, urinary tract, gastrointestinal and uncomplicated gonococcal infections (Jones, 1993; Galova *et al*, 1996; Pichichero, 1997; Mandel *et al*, 1996). Ceftibuten was very efficacious against all enteropathogens in this study, similar to the fact found in previous studies that *Salmonella* spp and *Shigella* spp were very susceptible to ceftibuten (Jones and Barry, 1988; Jones, 1993; Bauernfeind, 1991; Verbist *et al*, 1991). Ceftibuten is as effective as cotrimoxazole in the treatment of diarrhea caused by *Shigella* and entero-invasive *Escherichia coli* in children (Prado *et al*, 1992). This study showed the success of ceftibuten and norfloxacin in treatment of *Salmonella* and *Shigella* gastrointestinal infections and the equivalence of their efficacy. A previous study reported ceftibuten's adverse effects, including diarrhea and vomiting (Reidenberg, 1995), while none of these were found in this study.

In conclusion, this prospective, randomized study demonstrated that ceftibuten is safe and as good as norfloxacin in treatment of acute gastrointestinal infection in children. It has a good taste and

Table 5
Outcome of therapy in patients with acute gastrointestinal infection caused by *Salmonella* and *Shigella* in both study groups.

Outcome	Ceftibuten N = 20	Norfloxacin N = 22	p-value
Salmonella			
Clinical success (days)	2.7	2.2	> 0.05
Range (days)	2-4	2-3	
Shigella			
Clinical success (days)	2.3	2.0	> 0.05
Range (days)	1-3	1-3	

is convenient to use in oral suspension form. In the developing countries, in which multiple-drug-resistant strains are prevalent, ceftibuten may be the drug of choice in treating *Shigella* and *Salmonella* gastroenteritis especially in immunocompromised children. Ceftibuten may be considered for use as a single drug or intravenous oral step down in treating community-acquired respiratory tract, urinary tract, or uncomplicated gonococcal infections with invasive gastrointestinal tract infections. However, the selection of drugs for children should be based on the severity of disease, as well as the safety, acceptance and cost of drugs.

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