

Therapeutic Efficacy of Cefdinir in Community-acquired Infections

Amorn Leelarasamee, M.D.*

Panpit Suwangool, M.D.**

Somsak Lolekha, M.D.***

Abstracts

Therapeutic efficacy of cefdinir, a new oral third-generation cephalosporin, was evaluated objectively in Thai patients with community-acquired respiratory tract infection, urinary tract infection, skin and soft tissue infection as well as gastrointestinal tract infection. The study was an open-label, multi-center design and was carried out during March to November 1995. A total of 168 patients of whom 104 patients were female, was enrolled with average age of 43.5 years old. Cefdinir was administered orally 100 mg three times a day for 5-7 days. Major causative pathogens were *E. coli* (22.7%) streptococci (15.9%) and klebsiella (15.9%). The cure rate and improvement were seen in 79.2 and 17.5 percent of the patients respectively. Only 3.3 percent was considered treatment failure. The pathogens were eradicated in 77.9 percent and incompletely eliminated in 14.7 percent. Persistence of pathogens was found in 2.9 percent, and relapse of the same pathogens in 4.4 percent. If cefdinir was used as sequential (switch) therapy, it was calculated that cefdinir could cut treatment cost on average by 6,094 bahts per case. Adverse reactions were found in 3.8 percent, most of which were mild such as nausea, abdominal discomfort and dizziness. It was concluded that cefdinir was well tolerated and was an useful oral antimicrobial for treatment of mild community-acquired bacterial infections in Thai patients. (*J Infect Dis Antimicrob Agents* 1997;14:67-70.)

INTRODUCTION

Cefdinir, a new third-generation oral cephalosporin, structurally differs from cefotaxime by composing an hydroxyimino-aminothiazole instead of a methoximino-aminothiazole side chain at position 7 and a vinyl group at position 3. These changes renders cefdinir possess the characteristics of third-generation cephalosporin which in general, exhibit high affinity for penicillin-binding protein (PBPs) and greater stability against beta-lactamases (1). In addition, administration by oral route is made possible by the vinyl group (2). Its *in vitro* anti-bacterial activity

studied in Thailand confirms the results reported from abroad that cefdinir is the only third-generation oral cephalosporin that retains activity against gram-positive bacteria (3,4) while other oral third-generation cephalosporins loose this activity in order to trade-off for excellent antimicrobial activity against gram-negative bacteria (5). It also possesses post-antibiotic effect against both gram-positive and some gram-negative micro-organisms (1) whereas most other oral cephalosporins lacks this activity against the latter. Cefdinir also demonstrates synergy with polymorphonuclear neutrophils and serum to increase the

*Division of Infectious Diseases, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700.

**Division of Infectious Diseases, Department of Medicine, Chulalongkorn University, Bangkok 10330.

***Division of Infectious Diseases, Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

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Reprint request : Division of Infectious Diseases, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

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susceptibility of *E. coli* and *S. aureus* *in vitro* (1).

Cefdinir, with its dosage of 100 mg, achieves a plasma concentration of 1.1 mg/l which is consistently in excess of MICs for various pathogens commonly responsible for community-acquired infections such as *S. pneumoniae*, *H. influenzae*, *K. pneumoniae* and *M. catarrhalis*. Various studies have been published to confirm its effectiveness in respiratory tract, otolaryngological, urinary tract, skin and soft tissue infections (6,7). A pilot therapeutic study has been conducted in 30 patients with respiratory tract infections at Chulalongkorn Hospital in 1994 with overall excellent clinical and bacteriological responses. Thus, the well-balanced and broad spectrum activities with beta-lactamase stability of cefdinir deserved a further appraisal of its clinical usefulness and tolerability in a wider scale in various community-acquired infections. The study also evaluated its potential use in antimicrobial sequential therapy (switch therapy) whenever possible.

MATERIALS AND METHODS

This study was an open-label, multi-centered study. Patients of both sexes with various community-acquired infections possibly due to bacterial etiology, were recruited from various hospitals located in Bangkok and upcountry areas during March to November 1995. Infections due to bacteria resistant to current antimicrobial use but sensitive to cefdinir was also included. Moderately septic or terminally ill patients, those with severe renal and hepatic impairment as well as pregnant and nursing women were excluded or if in the investigator's opinion, were not anticipated to comply with protocol requirements. Other exclusion criteria were patients who had been receiving other antimicrobials, were infected with cefdinir-resistant pathogens, gave a history of hypersensitivity or intolerance to penicillins or cephalosporins, exhibited clinical syndrome due to viral infections or infection-like allergy symptoms of respiratory tract disorders. Gram-staining and bacterial culture were performed if clinical specimens were obtainable. In case of lower respiratory tract infection, diagnosis was ascertained by gram-stain of sputum which should show > 25 pus cells/LPG and predominant bacteria could be identified. To diagnose pneumonitis, pulmonary infiltration must be demonstrated using chest roentgenography.

Cefdinir was orally administered at the dose of one 100 mg capsule three times a day before meals for 5-7 days. The drug was supplied by Fujisawa Pharmaceutical Co., Ltd. Prior to administer cefdinir, all antimicrobial medication were withdrawn. If there was no improvement or patient's status deteriorated after 3-5 day therapy with

cefdinir, rescue medication would be instituted with antimicrobials known for treatment of the particular infections.

Assessment of treatment was done according to both clinical efficacy and microbiological evaluation. Complete resolution of clinical signs and symptoms of infection was considered as cure. Improvement meant incomplete resolution of the clinical feature. Failure meant persistence of those signs and symptoms after 3-5 day therapy. Microbiological evaluation was classified as elimination if original pathogen was no longer present; reduction if presence of original pathogen to lesser number or elimination of at least one of multiple pathogens; persistence if no reduction of original pathogen and relapse if recurrence of the same pathogen within one week after the end of treatment. Any adverse events suspected due to cefdinir therapy were reported. Economic consideration was performed if cefdinir was used as sequential therapy by calculating quantitative difference of duration of hospitalization and drug treatment cost between administering parenteral antimicrobial alone and parenteral antimicrobial followed by cefdinir after clinical symptoms recovered. Patient report form was completely filled up with the result of each patient and sent to principal investigator for data analysis.

RESULTS

One hundred and sixty-eight patients (64 men and 104 women) were enrolled in the study. The mean age was 43.5 years (range, 1 to 90 years; standard deviation, 20.1 years). Upper and lower respiratory tract infections accounted for 78 and 53 cases respectively. Urinary tract infection was found in 26 cases and skin and soft tissue infection in 5 cases. Details of all diagnoses were showed in Table 1. Eighty-eight patients underwent microbiological investigation and the causative pathogens were identified as summarized in Table 2. Of these, *E. coli*, streptococci, klebsiella, *H. influenzae* and staphylococci were the five most common micro-organisms which were isolated in 22.7, 15.9, 15.9, 6.8 and 5.7 percent respectively. When clinical efficacy was evaluated, it was found that 154 of the total 168 patient report forms were considered scientific valid for data analysis. Cure was seen in 79.2 percent of the patients, whereas improvement in 17.5 percent and treatment failure in 3.3 percent as summarized in Fig. 1. The bacteriological evaluation of cefdinir therapy has, then, been evaluated as complete elimination of original pathogens in 77.9 percent of the patients and reduction of original pathogens to lesser number in 14.7 percent, whereas only

Table 1. Type and number of illness among participants.

Type of Illness	n	(%)
Upper respiratory tract (URI)	78	(46.4)
Pharyngitis	12	
Pharyngo-tonsillitis	10	
Tonsillitis	21	
Laryngitis	2	
Sinusitis	13	
Otitis media	10	
Abscess in external auditory canal	1	
URI	9	
Lower respiratory tract	53	(31.5)
Bronchitis	29	
Pneumonia	24	
Urinary tract	26	(15.5)
Cystitis	5	
Pyelonephritis	7	
Urinary tract infection	14	
Skin and soft tissue	5	(3.0)
Pyoderma	1	
Infected wound	2	
Cellulitis	1	
Lymphadenitis	1	
Gastro-intestinal tract	5	(3.0)
Peritonitis	1	
Acute appendicitis	1	
Dysentery	1	
Diverticulitis	1	
Retroperitoneal abscess	1	
Sepsis 1	(0.6)	
Total	168	(100)

2.9 and 4.4 percent were unable to reduce the original pathogens and exhibited recurrence of the same pathogens within one week respectively after the end of treatment as showed in Fig. 2. Only 20 patients received cefdinir as a substitute for parenteral cephalosporin after the patients' infections were kept under control. Eventhough difference of hospitalization cost existed among study centres from which highly fragmented information was obtained, the attempt has been made to average the cost saving of this sequential or "switch" therapy procedure. It was found that an average hospital cost saving at 6,094 bahts per case was achieved in the study. With regard to adverse reaction, 159 patient report forms were evaluable. Only six cases (3.8%) were reported to have adverse drug

Table 2. Types and numbers of isolated micro-organisms.

Microorganisms	n	(%)
<i>E. coli</i>	20	(22.7)
Klebsiella	14	(15.9)
Streptococci	14	(15.9)
<i>H. influenzae</i>	6	(6.8)
Staphylococci	5	(5.7)
<i>P. aeruginosa</i>	5	(5.7)
<i>P. mirabilis</i>	3	(3.4)
Gram-negative bacilli	2	(2.3)
Shigella	1	(1.1)
Acinetobacter	1	(1.1)
Enterobacter	1	(1.1)
Normal flora	12	(13.6)
No growth	4	(4.5)
Total	88	(100)

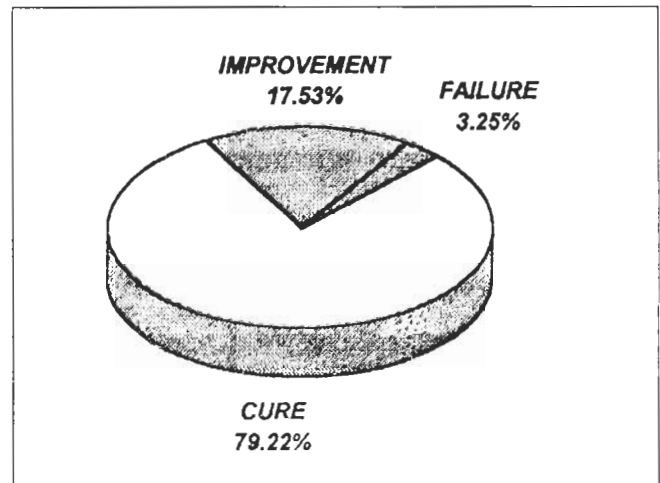


Fig. 1 Clinical efficacy of cefdinir.

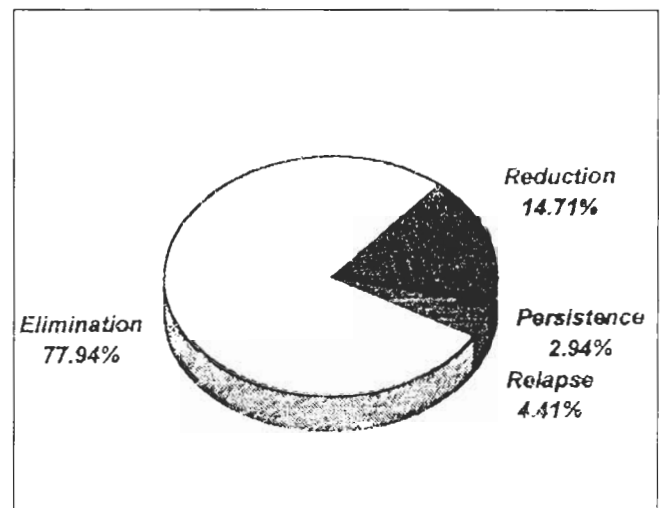


Fig. 2 Bacteriological efficacy of cefdinir.

reactions. The side effects included gastrointestinal disturbance i.e., nausea, abdominal discomfort in 3 cases and dizziness for the rest. All of these adverse drug reactions was mild, transitory and thus it was not necessary to withdraw the studied drug. They disappeared without any treatment after the end of cefdinir therapy.

DISCUSSION

In this study, therapeutic efficacy of cefdinir was explored in respiratory tract, gastrointestinal tract, urinary tract, skin and soft tissue infections which are among the four most common causes of community-acquired infections that are suitable to be treated as out-patient basis with an oral antimicrobial if indicated. To assess the true value of cefdinir in upper respiratory tract infection (URI), it is necessary to know the likely frequency of all bacterial causes of the infection *versus* that of viral causes since most physicians felt inclined to prescribe an antimicrobial for any patient with URI (8). Many throat swab cultures in patients with URI in the study turned out to be normal flora or no growth which compromise the validity of therapeutic assessment of URI. It was conceivable that our study patients were contaminated with many cases of viral URI which recovered spontaneously and would account for the overall high efficacy of the drug. For lower respiratory tract infection, ascertainment of infection was done using gram-stain of sputum and *H. influenzae* was isolated in 6 cases though *S. pneumoniae* should have also been isolated. Among 26 cases with urinary tract infection, cefdinir was used as sequential therapy in 7 cases who were diagnosed as pyelonephritis and parenteral antimicrobial was empirically, given. In gastrointestinal infection cefdinir was administered when an antimicrobial to combat gram-negative enteric bacilli was needed, together with an antimicrobial against anaerobic infection. When patients' conditions were rather stable. The overall clinical efficacy was calculated to be 79.2 percent and improvement 17.5 percent. Microbiological success was observed in 77.9 percent and reduction in 14.7 percent while persistence of the original bacteria was found in 2.9 percent and relapse in 4.4 percent. The study results support the use of cefdinir as outpatient therapy, which is convenient, economical and patient preferred. Cefdinir can also be used as a sequential therapy for cefdinir-sensitive pathogenic bacteria in hospitalized patients and remains a convenient maintenance treatment option for those with stable condition following appropriate parenteral therapy, or for whom the risk of more rapid progression is balanced by the benefit associated with avoiding daily intravenous infusions. Hospital cost saving was estimated to be 6,094 bahts per case when

parenteral drug was substituted with cefdinir in case of sequential therapy.

Adverse reaction of cefdinir was found to be small in the study. This was attributed in part to criteria of exclusion which did not allow patients with potential adverse reaction to cefdinir to enter the study. Gastrointestinal symptoms were common conditions which are sometimes difficult to distinguish its cause due to others from cefdinir especially in a descriptive study design like this one. However, cefdinir should not also be administered in neutropenic patient and as a general rule for a cephalosporin, dose adjustment should be made based on renal function in patient with renal insufficiency.

In conclusion, cefdinir is a new oral third-generation cephalosporin which is highly active against both gram-positive and gram-negative community-acquired bacteria. It was ideal to be used in office, clinic, home health care, nursing home to treat mild community-acquired infections in various systems. In addition to proven efficacy, cefdinir capsules provide a manageable safety profile, ease of administration and increased convenience. However, there is a pressing need for any new drug to be used rationally to avoid the rapid development of multiple-drug-resistant community-acquired pathogens (9). Further clinical evaluation of cefdinir in a wider scale and monitoring of its susceptibility pattern as well as safety profile are warranted.

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