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Comparison of Cefdinir and Cefaclor in Treatment of Community-Acquired Pneumonia

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Six hundred ninety patients were enrolled in a multicenter, randomized, double-blind trial comparing the efficacy and safety of cefdinir with those of cefaclor in the treatment of community-acquired pneumonia. Patients received either 10 days of treatment with cefdinir ($n = 347$) at 300 mg twice daily or 10 days of treatment with cefaclor ($n = 343$) at 500 mg three times daily. Microbiological assessments were performed on sputum specimens obtained at admission and at the two posttherapy visits, if available. Respiratory tract pathogens were isolated from 538 (78%) of 690 patient admission sputum specimens, with the predominant pathogens being *Haemophilus parainfluenzae*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*. The microbiological eradication rates at the test-of-cure visit were 92% (238 of 260 pathogens) and 93% (245 of 264 pathogens) for the evaluable patients treated with cefdinir and cefaclor, respectively. A satisfactory clinical response (cure plus improvement) was achieved in 89% (166 of 187) and 86% (160 of 186) of the evaluable patients treated with cefdinir and cefaclor, respectively. Except for the incidence of diarrhea, adverse event rates while on treatment were equivalent between the two treatment groups. Diarrhea incidence during therapy was higher for patients treated with cefdinir (13.7%) than for patients treated with cefaclor (5.3%). These results indicate that cefdinir is effective and safe in the treatment of patients with pneumonia.

Despite the ongoing development of more-potent antibacterial agents and improvements in diagnostic and investigational techniques, pneumonia remains an important disease (5, 25). It was the sixth leading cause of death in the United States over the period 1991 to 1993 (27) and is the leading cause of death from infectious diseases (25). It is the fourth leading cause of death in the elderly (16). The disease has an incidence rate in the United States of 7 to 14 per 1,000 patients at risk per year (21) and affects 2.5 million (19) to as many as 4 million patients per year (25). Adult hospital admissions due to pneumonia range from more than 500,000 (1) to 800,000 (25) per year. Disease prevalence is higher in the elderly (12, 13); in those with underlying pulmonary or chronic diseases, such as chronic obstructive pulmonary disease (17, 25); in certain ethnic groups (14); and in the immunocompromised (17, 20).

Over the last several decades, the microbiology of community-acquired pneumonia (CAP) appears to have changed (22). Earlier studies reported *Streptococcus pneumoniae* to be by far the most prevalent pathogen (20). Recent studies, however, have shown that other pathogens have become increasingly more significant (1, 2, 5, 12, 20). These include *Haemophilus influenzae* (15), *Moraxella catarrhalis* (10), *Staphylococcus aureus* (20), *Haemophilus parainfluenzae* (28), aerobic gram-negative bacilli (20), and viruses (3) as well as *Legionella*, *Chlamydia*, and *Mycoplasma* (10). However, in as many as 49 to 60% of the cases, the microbial etiology of the disease remains uncertain (3, 10).

Cefdinir (CI-983, FK482) is a semisynthetic, broad-spectrum oral cephalosporin antibiotic intended for use in the treatment of mild to moderate bacterial infections (8). It is stable against many β-lactamase enzymes (8). The increasing prevalence of β-lactamase in pathogens such as *Haemophilus* spp. and *M. catarrhalis* makes stability to these enzymes an important consideration in the treatment of respiratory tract infections. In vitro microbiology studies have shown the compound to be microbiologically active against streptococci, *S. aureus*, *Haemophilus* spp., *M. catarrhalis*, and most gram-negative enteric bacteria (8). This report describes the results of a clinical study comparing the efficacy and safety of cefdinir with those of cefaclor in patients with CAP.

MATERIALS AND METHODS

Patient selection. This double-blind, prospective, randomized study was conducted at 48 centers in the United States from December 1991 through January 1995. The patients enrolled in the study were those with a diagnosis of CAP, confirmed by chest X ray; were at least 13 years old and of either sex; and presented with a cough and sputum production. Women who were of childbearing potential were required to have a negative urine pregnancy test. Patients were excluded from the study if they were pregnant or lactating, had concomitant diseases which may have precluded proper assessment of the disease under study, had hepatic disease or obstruction of the biliary tract, had a baseline serum creatinine level greater than two times the upper limit of normal or a known creatinine clearance rate of <30 ml/min, were allergic to β-lactam antibiotics, had concomitant infections requiring systemic antibacterial therapy, received any other investigational compound within 4 weeks before entering this study, participated in any other cefdinir study, were receiving probenecid or iron-containing supplements, or took an antibiotic within 7 days prior to anticipated study admission. All investigators received Institutional Review Board approval before enrolling any patient, and all patients (or their guardians) provided written informed consent before study entry. The study was conducted according to the Declaration of Helsinki.

Microbiological investigations. All patients were required to produce a sputum specimen at study entry. Those specimens which contained >25 neutrophils and ≤10 epithelial cells per low-power (100×) microscopical field were to have been submitted for culture. A central laboratory (SciCor, Inc., Indianapolis, Ind.) performed cultures and susceptibility testing. Susceptibility testing was performed according to the then-current procedures specified by the National Committee for Clinical Laboratory Standards (23, 24). Cefdinir was tested by the disk-agar diffusion (with a 5-μg disk) and microdilution (with Sensititre plates) methodologies. Cefaclor was tested by microdilution methods only. For disk-agar diffusion, susceptibility was defined as a zone diameter of ≥20 mm, intermediate susceptibility was defined as a zone diameter of 17 to 19 mm, and resistance was defined as a zone diameter of ≤16 mm (18). For cefdinir testing by the microdi-

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TABLE 1. Patient characteristics

Variable	Value for group	
	Cefdinir	Cefaclor
No. of patients	347	343
Sex (no. [%])		
Male	193 (55.6)	192 (56.0)
Female	154 (44.4)	151 (44.0)
Race (no [%])		
White	298 (85.9)	288 (84.0)
Black	32 (9.2)	44 (12.8)
Asian	3 (0.9)	1 (0.3)
Other[a]	14 (4.0)	10 (2.9)
Age (yr)		
Median	44.0	44.0
Range	13.0–89.0	13.0–93.0
Distribution (no. [%])		
13 to <18	10 (2.9)	8 (2.3)
18 to <65	255 (73.5)	263 (76.7)
≥65	82 (23.6)	72 (21.0)

[a] Hispanic, Filipino, American Indian, and Brazilian.

lution methodology, susceptibility was defined as an MIC of ≤1 μg/ml, intermediate susceptibility was defined as an MIC of 2 μg/ml, and resistance was defined as an MIC of ≥4 μg/ml. Published standards were used for the cefaclor susceptibility breakpoints. Appropriate strains (*Haemophilus* spp. and *M. catarrhalis*) were also tested for β-lactamase production with nitrocefin disks.

Antimicrobial therapy. Patients were assigned a study medication with a computer-generated randomization schedule, either cefdinir at 300 mg twice daily or cefaclor at 500 mg three times daily (1:1). All medication was packaged in capsules in a double-blind, double-dummy fashion. Each patient was instructed to take four capsules three times per day for 10 days without regard to meals. Due to a possible cefdinir interaction with Mg- and Al-containing antacids, patients were requested to withhold antacid therapy for 2 h before and after study medication dosing. The investigator, the patient, and the sponsor did not know to which regimen the patient was randomized until after all patients had completed the study and all assessments had been determined.

Clinical, microbiological, and safety assessments. Assessments were performed for each patient at the admission (study entry) visit, on study days 3 to 5, at 6 to 14 days posttherapy (the test-of-cure [TOC] visit), and at 21 to 35 days posttherapy (the long-term follow-up [LTFU] visit). The clinical signs and symptoms of cough, sputum production, dyspnea, and chest pain were graded as absent, mild, moderate, or severe. Chest sounds (rales, rhonchi) were graded as absent or present. Temperatures were recorded. Sputum was collected for culture at the admission visit and, if available, at subsequent visits. Blood and urine were collected for safety testing at the admission visit and at the TOC visit. If abnormalities were seen at the TOC visit, a repeat safety test was to have been performed at the LTFU visit. A brief physical examination was performed at study entry and at both of the posttherapy visits. Patients were queried in a nonspecific fashion for adverse events at each visit (6).

Early termination. Patients could be eliminated from the study at their request, at that of the investigator, or at that of the sponsor.

Efficacy criteria. Overall clinical efficacy was assessed at the TOC and LTFU visits. Clinical success was defined as cure (absence or satisfactory remission of all admission signs and symptoms) plus improvement (satisfactory remission but not complete disappearance of admission signs and symptoms). Failure was defined as worsening or lack of significant remission of signs and symptoms. Recurrence was defined as a worsening of signs and symptoms at the LTFU after a clinical success at the TOC visit. Microbiologically, admission pathogens which were not present at the follow-up visit were classified as eradicated, and those that remained were defined as persistent. If clinical improvement occurred such that no sputum was available for culture at follow-up visits, the pathogen was presumed to have been eradicated. A superinfection was defined as the appearance of a new pathogen between the admission and TOC visits with a concomitant worsening of clinical condition. A reinfection was any new pathogen seen between the TOC visit and the LTFU visit, again with an accompanying worsening of clinical condition.

Evaluability criteria. Patients were classified as evaluable if the admission chest X ray indicated a pulmonary infiltrate or consolidation, at least one respiratory tract pathogen was isolated from the admission sputum specimen, each respiratory tract pathogen isolated at admission was susceptible to both study drugs, clinical and microbiological assessments were available 6 to 14 days posttherapy (except for failures prior to this visit), no nonstudy antimicrobials were given in the 7 days before the beginning of this study, at least 8 days of study medication were taken, no concurrent systemic antimicrobials were taken, there were no concurrent infections which could have confounded the assessment of pneumonia, and there was no intentional randomization violation. Qualified patients were those who were evaluable at the TOC visit and returned for assessment at the LTFU visit without protocol violations.

Statistical analyses. The sample size of this study was designed to demonstrate equivalence of the treatment groups by a confidence interval (CI) approach. Assuming an average clinical response rate of 90%, 190 evaluable patients per treatment group provides an 80% power to prove equivalence with a 95% CI. Confirmatory Cochran-Mantel-Haenszel tests were performed to detect treatment differences with respect to adverse event rates, diarrhea rates, and rates of discontinuation of study medication due to adverse events. All statistical testing was performed with SAS software.

RESULTS

Of the 690 patients entered, 347 were randomized to the cefdinir group and 343 were randomized to the cefaclor group. Patients were evenly distributed by sex, race, age, and presence and severity of clinical signs and symptoms across both treatment groups. A sizable number of patients in both treatment groups were elderly (Table 1).

The median patient exposure was 10 days for all patients randomized to each study medication.

The presence and severity of clinical signs and symptoms at study admission were similar for the patients in the two treatment groups (Table 2).

Of the 690 patients enrolled, 538 patients (78%) had at least one respiratory tract pathogen isolated from the admission sputum specimen. Study drug susceptibilities for the most prevalent of these isolates are shown in Table 3. At admission, 2% (15 of 771) of the pathogens were resistant to cefdinir and 3% (23 of 770) were resistant to cefaclor. Significantly more admission pathogens were resistant to cefaclor than to cefdinir

TABLE 2. Clinical signs and symptoms at admission

Sign or symptom	Severity	No. (%) of patients[a]	
		Cefdinir	Cefaclor
Cough	Mild	45 (13)	32 (9)
	Moderate	211 (61)	209 (61)
	Severe	88 (25)	98 (29)
	Absent	0 (0)	1 (0.3)
Sputum production	Mild	91 (26)	94 (27)
	Moderate	195 (56)	184 (54)
	Severe	58 (17)	61 (18)
	Absent	0 (0)	1 (0.3)
Shortness of breath	Mild	133 (38)	123 (36)
	Moderate	123 (36)	123 (36)
	Severe	32 (9)	32 (9)
	Absent	56 (16)	62 (18)
Chest pain	Mild	130 (38)	129 (38)
	Moderate	93 (27)	98 (29)
	Severe	20 (6)	13 (4)
	Absent	101 (30)	100 (29)
Chest sounds	Present	327 (94)	326 (95)
	Absent	17 (5)	14 (4)
Fever	Mild	46 (13)	49 (14)
	Moderate	12 (4)	15 (4)
	Severe	1 (0.3)	4 (1.2)
	Absent	284 (82)	271 (79)

[a] There were 347 patients in the cefdinir group and 343 patients in the cefaclor group.

TABLE 3. Susceptibilities of the most prevalent admission pathogens to cefdinir and cefaclor

Pathogen and characteristic	No. of isolates	Antimicrobial agent	MIC (μg/ml)[a]		
			50%	90%	Range
H. influenzae					
β-Lactamase negative	138	Cefdinir	0.5	1.0	0.01–2.0
		Cefaclor	2.0	4.0	0.03–16.0
β-Lactamase positive	40	Cefdinir	0.5	1.0	0.12–2.0
		Cefaclor	2.0	8.0	0.5–32.0
Haemophilus parahaemolyticus	33	Cefdinir	0.03	0.25	0.01–0.25
		Cefaclor	0.25	1.0	0.12–16.0
H. parainfluenzae					
β-Lactamase negative	209	Cefdinir	0.25	0.5	0.01–2.0
		Cefaclor	2.0	4.0	0.03–64.0
β-Lactamase positive	12	Cefdinir	0.25	0.5	0.12–2.0
		Cefaclor	2.0	4.0	0.12–8.0
Klebsiella pneumoniae	34	Cefdinir	0.12	0.25	0.06–0.5
		Cefaclor	1.0	1.0	0.5–4.0
M. catarrhalis					
β-Lactamase negative	1	Cefdinir	NA[b]	NA	0.06
		Cefaclor	NA	NA	0.12
β-Lactamase positive	26	Cefdinir	0.12	0.25	0.12–0.25
		Cefaclor	0.5	1.0	0.25–2.0
S. aureus	60	Cefdinir	0.5	1.0	0.12–16.0
		Cefaclor	2.0	8.0	0.5–64.0
S. pneumoniae	88	Cefdinir	0.12	0.50	0.01–16.0
		Cefaclor	1.0	4.0	0.03–64.0

[a] 50% and 90%, MICs at which 50 and 90% of the isolates are inhibited, respectively.
[b] NA, not applicable.

($P = 0.033$). Twenty-two percent of the *H. influenzae*, 5% of the *H. parainfluenzae*, and 96% of the *M. catarrhalis* isolates obtained at admission were β-lactamase producers.

Although most patients in this study were treated on an outpatient basis, five patients in the cefdinir arm and six in the cefaclor arm were hospitalized due to pneumonia.

Efficacy. Of the 690 randomized patients, 373 patients were evaluable, 187 in the cefdinir arm and 186 in the cefaclor arm. Table 4 presents the microbiological and clinical efficacy outcomes at TOC for these patients. Clinical success (cure plus improvement) was seen in 89 and 86% of the evaluable patients treated with cefdinir and cefaclor, respectively. The clinical success rates were equivalent by the 95% CI approach (95% CI = −7.6 to 8.9%). The overall rates of microbiological eradication of pathogens were 92% for cefdinir patients and 93% for cefaclor patients, again equivalent by CI testing (−5.9 to 3.3%). Table 4 also presents microbiological eradication data at TOC for the most-prevalent pathogens.

Patients were most frequently excluded from the evaluable subset because no respiratory tract pathogen was isolated from the baseline sputum specimen (78 cefdinir patients, 74 cefaclor patients). Other prevalent reasons included clinical assessments performed outside of the protocol-specified time windows and microbiological assessments performed outside of the time window, both occurring in similar numbers for both treatment groups. Patients could have been excluded for more than one reason.

Among qualified patients who had all admission pathogens eradicated at the TOC visit, the rates of microbiological eradication of pathogens at the LTFU visit were 99% (164 of 165) for the cefdinir group and 100% (189 of 189) for the cefaclor group.

Twelve cefdinir patients (4%) and 20 cefaclor patients (6%) experienced superinfections. The most prevalent superinfecting pathogen was *H. parainfluenzae* in both treatment groups (cefdinir, 6 patients; cefaclor, 11 patients). None of the superinfecting *H. parainfluenzae* isolates was resistant to either study drug, and all but two isolates were β-lactamase negative. Reinfections were seen in two patients in the cefdinir arm and one patient in the cefaclor arm.

Four cefdinir-treated patients satisfied all evaluability criteria except that they had at least one admission pathogen which was susceptible to cefdinir and resistant to cefaclor. Cefdinir eradicated all six cefdinir-susceptible, cefaclor-resistant admission pathogens from these patients at the TOC visit. All four patients were assessed as clinical successes.

Safety assessments. Safety data were analyzed for all patients who received study medication. Of these patients, 121 (35.2%) patients receiving cefdinir and 87 (25.6%) patients receiving cefaclor experienced at least one adverse event during treatment ($P = 0.005$). Seventy-three (21.2%) of the patients treated with cefdinir and 52 (15.3%) of the patients treated with cefaclor experienced at least one adverse event during the treatment phase which the investigator considered to be drug related ($P = 0.027$).

The most frequent adverse events on therapy were diarrhea (13.7 and 5.3% for cefdinir- and cefaclor-treated patients, respectively), headache (5.5 and 3.5%), nausea (3.2 and 1.5%), vomiting (2.0 and 0.9%), and rash (1.5 and 1.8%). The difference for diarrhea was statistically significant ($P < 0.001$). There was no difference in adverse events on therapy, other than for diarrhea, between the treatment groups ($P = 0.253$).

Six patient deaths occurred during the study, three in each treatment arm. None was related to study medication.

Twenty-one (6%) patients treated with cefdinir and 14 (4%) treated with cefaclor discontinued treatment due to an adverse event ($P = 0.334$). The most common adverse events providing reasons for discontinuing cefdinir were diarrhea, nausea, and vomiting; the most common of such events for cefaclor was rash.

Review of the physical examination changes at TOC and at admission revealed no evidence of toxicity. Similarly, review of the clinical laboratory changes from admission to the TOC visit showed no changes except for a trend toward lower leukocyte

TABLE 4. Efficacy rates in evaluable patients at the TOC visit

Efficacy parameter	Value for group			
	Cefdinir		Cefaclor	
	n/N[a]	%	n/N	%
Clinical success	166/187	89	160/186	86
Microbiological eradication of:				
H. influenzae	55/65	85	60/72	83
H. parainfluenzae	81/89	91	78/82	95
M. catarrhalis	10/10	100	11/11	100
S. pneumoniae	31/31	100	35/35	100
Other	61/65	94	61/64	95
Total	238/260	92	245/264	93

[a] n/N (clinical), number of successes/number of patients; n/N (microbiological), number of pathogens eradicated/number of pathogens isolated.

and polymorphonuclear leukocyte counts for both treatment groups.

DISCUSSION

This study demonstrates that in patients with radiologically documented CAP, the broad-spectrum oral cephalosporin cefdinir was equivalent in terms of clinical outcome and microbiological eradication rate to cefaclor, an expanded-spectrum cephalosporin.

Our results compare favorably with those obtained in a study involving pneumonia patients treated with loracarbef (16). In that study a favorable clinical response (cure or improvement) was seen in 100% of the patients treated with loracarbef and 92% of the patients treated with the comparative agent, amoxicillin-clavulanate. Pathogen eradication in evaluable patients was 97% in loracarbef-treated patients and 92% in amoxicillin-clavulanate-treated patients. One explanation for the difference between outcomes may be methodologic differences between the studies: Hyslop et al. (16) assessed microbiological and clinical efficacy in the 3 days immediately following treatment, while the present study determined efficacy 6 to 14 days posttherapy. The assessment of efficacy shortly after the end of treatment may not have allowed inhibited pathogens or clinical symptoms to reappear, thus increasing the observed response rates. In contrast, in this study suppressed pathogens or clinical symptoms were more likely to reappear in the 6 to 14 days after completion of study medication.

Chien et al. (7) compared the efficacy of clarithromycin to that of erythromycin in patients with CAP. They reported a 97% (89 of 92) clinical success rate at the posttreatment assessment for evaluable patients receiving clarithromycin and a 96% (78 of 81) clinical success rate for erythromycin-treated patients. However, as in the study by Hyslop et al. described above, Chien et al. assessed clinical efficacy immediately after the completion of therapy, within 48 h. They reported that only 43 of 175 evaluable patients (25%) had positive admission cultures. In the clarithromycin group, 88% (23 of 26) of the admission isolates were eradicated at the posttreatment assessment compared to 100% (17 of 17) in the erythromycin group. Twenty-seven additional pathogens were identified by serologic studies; microbiological outcomes for these pathogens were not reported. We did not perform serologic analyses in the present study.

This is the first report of the treatment of CAP with cefdinir. The outcomes in cefaclor-treated patients in the present study are similar to those previously reported (5). A favorable clinical response (cure or improvement) was seen in 43 of 45 (95.6%) evaluable patients treated with cefaclor compared with 37 of 40 (92.5%) patients treated with the comparative agent, advanced-formulation cefaclor. Favorable bacteriologic response rates (pathogen eradicated or presumed eradicated) in the same patients were 86.7 and 87.5%, respectively. As above, clinical and bacteriological responses in this study were assessed within 72 h of completing therapy.

Recent reports suggest that the prevalence of ampicillin-resistant *H. influenzae* is increasing (10, 11). Farley et al. (11) reported that 16 of 45 isolates (36%) from patients with invasive *H. influenzae* disease were ampicillin resistant. Out of the total of 187 *H. influenzae* isolates obtained at admission in this study, 43 isolates (23%) were ampicillin resistant (zone diameter $\leq$ 18 mm). Four of these ampicillin-resistant *H. influenzae* isolates were β-lactamase negative. Forty-two of these ampicillin-resistant *H. influenzae* isolates were susceptible (or intermediately susceptible) to both cefdinir and cefaclor (one isolate was not tested against cefdinir; one isolate was resistant to cefaclor).

Resistance of *S. pneumoniae* to penicillin appears to be an increasing problem. In a recent large-scale surveillance study by Breiman et al., resistance to penicillin, defined as an MIC of $\geq$0.12 μg/ml, was detected in 6.6% of the isolates (4). In the present study, penicillin MICs for 13 of 91 (14%) admission isolates of *S. pneumoniae* were $\geq$0.12 μg/ml. For 11 of these, penicillin MICs were $\leq$1.0 μg/ml (intermediate); for the other two, penicillin MICs were $\geq$2 μg/ml (resistant). When tested against cefdinir, all 11 isolates intermediately susceptible to penicillin were susceptible (n = 9) or intermediately susceptible (n = 2) to cefdinir. The two isolates with high-level resistance to penicillin were also resistant to cefdinir (MICs of 8 and 16 μg/ml). When tested against cefaclor, all 11 isolates intermediately susceptible to penicillin were susceptible (n = 10) or intermediately susceptible (n = 1) to cefaclor. The penicillin-resistant isolates were also resistant to cefaclor (MICs of 16 and 64 μg/ml).

The incidence of adverse events experienced by patients while on treatment was higher for cefdinir patients than for those treated with cefaclor. This difference can be ascribed to diarrhea, for if diarrhea episodes are removed from the analysis, the adverse event incidence rates are comparable.

H. parainfluenzae was the most prevalent admission isolate from patients in this study. Traditionally, this organism has not been considered a respiratory tract pathogen. However, *H. parainfluenzae* is increasingly recognized as a pathogen in respiratory tract infections. Williams et al. (28) found that *H. parainfluenzae* was the second-most prevalent organism isolated from their patients. Poirier (26) found *H. parainfluenzae* to be a target pathogen in his study of CAP patients being treated with clarithromycin or roxithromycin. Additionally, *H. parainfluenzae* has been considered a pathogen in patients with other respiratory tract infections (9).

The incidence of fever in patients at the time of study admission is lower than one might expect. Explanations for this finding could include the relatively high proportion of elderly patients (approximately 30% were 60 years of age or older), who are less able to mount a febrile response to infection, and the 15% of study patients taking antipyretic medications at the time of presentation.

In this study, cefdinir and cefaclor were comparable for the treatment of CAP. Although the incidence of diarrhea was higher in cefdinir-treated patients, it was generally mild and did not lead to discontinuation of treatment. The increased antimicrobial activity of cefdinir compared to that of older agents and the increased convenience of twice daily dosing make cefdinir an attractive agent for the treatment of CAP.

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