Original Report

International Study Comparing Cefdinir and Cefuroxime Axetil in the Treatment of Patients with Acute Exacerbation of Chronic Bronchitis

C. L. A. Van Herwaarden, MD;* Charles E. Langan, MD;† Gerhard Siemon, MD;‡ Claus Rudolph, PhD;§ Constance H. Keyserling, MSc;¶ Mary Anne Nemeth, MA;¶ and Kenneth J. Tack, MD¶

ABSTRACT

Objectives: To assess the efficacy and tolerability of three antibiotic regimens in patients with acute exacerbation of chronic bronchitis.

Methods: In this double-blind, randomized, multicentered, parallel-group study, patients received once-daily cefdinir 600 mg, twice-daily cefdinir 300 mg, or twice-daily cefuroxime axetil 250 mg for 10 days. Primary efficacy measures were microbiologic eradication rate, by pathogen and by patient, and clinical response rate, by patient.

Results: Of 1045 patients, 589 were evaluable for efficacy. At baseline, most patients had moderate or severe cough and sputum production as well as rhonchi, wheezing, and dyspnea. The microbiologic eradication rates by pathogen were 90% with once-daily cefdinir, 85% with twice-daily cefdinir, and 88% with twice-daily cefuroxime. The corresponding values for microbiologic eradication rate by patient were 90% (once-daily cefdinir), 85% (twice-daily cefdinir), and 86% (twice-daily cefuroxime). The respective clinical response rates by patient were 81%, 74%, and 80%. There were no significant differences in the incidence of drug-related adverse events or discontinuations due to adverse events. Diarrhea was the most frequent complaint.

Conclusions: The results indicate that the efficacy and tolerability of cefdinir, once or twice daily, and cefuroxime were comparable with no significant differences between the regimens used.

*Medical Centre Dekkerswald, Groesbeck, The Netherlands; †Baillieston Health Centre, Glasgow, United Kingdom; ‡Fachklinik IVA, Donaustauf, Germany; §Parke-Davis International Clinical Development, Freiburg, Germany; and ¶Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan, USA.

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Address correspondence to Mary Anne Nemeth, JSI Communications, Le Moulin de Guiseuil, Loulans-Verchamp, F70230, France.

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Chronic bronchitis is a common respiratory disorder throughout the world. Defining features can range from daily coughs productive of sputum for 3 months per year over at least 2 consecutive years to advanced chronic obstructive airways disease.[1] Factors known to be associated with this disease include cigarette smoking, air pollution, socioeconomic status, and recurrent childhood respiratory infections.[2]

Acute exacerbation of chronic bronchitis (AECB) usually is associated with common respiratory pathogens, such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*, and may be particularly severe in the debilitated, in smokers, and in the elderly.[2–4]

Although most respiratory pathogens are susceptible to β-lactam-containing antibiotics, including penicillins and cephalosporins, the increasing prevalence of β-lactamase-producing organisms has increased the rate of resistance to established treatments.[5,6] The development of antibiotics that are stable in the presence of β-lactamase enzymes is of considerable importance.[7,8]

Cefdinir is a semisynthetic, extended-spectrum, third-generation cephalosporin antibiotic that is intended for use in the treatment of mild-to-moderate bacterial infections. The drug has good activity against typical respiratory tract pathogens such as *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*.[9] Cefdinir also is highly stable in the presence of β-lactamase enzymes; and many β-lactamase-producing bacteria that are resistant to penicillins, and some cephalosporins, are susceptible to cefdinir.[10,11] Cefuroxime is a second-generation cephalosporin with proven efficacy against the major pathogens of lower respiratory tract infections (LRTIs).[12] It has activity against β-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*, which are resistant to ampicillin or amoxycillin. Clinical studies have indicated that cefuroxime is effective and well tolerated in the treatment of AECB.[13]

The aim of this study was to evaluate the efficacy and safety of two dosages of cefdinir (600 mg once daily [o.d.] and 300 mg twice daily [b.i.d.]) with cefuroxime axetil (250 mg b.i.d.) administered for 10 days in patients with AECB.

MATERIALS AND METHODS

Patients were enrolled into this double-blind, randomized, parallel-group study from centers in Australia, Europe, South Africa, and the United States. Each center used a similar protocol that was approved by the local Ethics Committee or Institutional Review Board. The trial was carried out in accordance with the Declaration of Helsinki, and all patients gave written informed consent. The first patient was treated in November 1992 and the last follow-up visit was in January 1995.

Patients

At baseline, each patient's medical history was taken, and he or she underwent a physical examination, chest roentgenogram, clinical assessment, Gram stain, sputum culture and susceptibility testing, and clinical laboratory evaluations (hematology, blood chemistry, and urinalysis).

Patients were eligible if they were at least 13 years old (at least 18 y in Germany and two centers in the United Kingdom, and at least 21 y in one center in the United Kingdom) and had a history of chronic bronchitis and a current diagnosis of acute exacerbation of chronic bronchitis of presumptive bacterial origin. The diagnosis had to be accompanied by cough productive of mucopurulent or purulent sputum and a pretreatment sputum culture positive for a lower respiratory tract pathogen.

Patients were excluded in the following circumstances: evidence of pneumonia on a pre-screen roentgenogram; any disease or condition (e.g., cystic fibrosis, bronchiectasis, bronchial carcinoma, or pulmonary structure defects) likely to affect evaluation of the study medication; evidence of significant systemic disease (e.g., cardiovascular, gastrointestinal, psychiatric disease); hepatic or renal impairment; hypersensitivity to β-lactams; baseline pathogen known to be resistant to either study drug; concomitant infection requiring a systemic antibiotic; and use of a systemic antibiotic in the 48 hours (or 5 plasma half-lives) prior to starting treatment.

Patients could enter the study before the results of the pretreatment sputum culture and susceptibility tests were known. Those with cultures negative for lower respiratory tract pathogens or showing resistant pathogens could be withdrawn from the study and treated appropriately if failing, or remain in the study if in the opinion of the investigator there was satisfactory clinical improvement. However, such patients were not considered evaluable.

Pathogens

The genus and species of all pathogens isolated from cultures were identified. The individual investigators together with the microbiologist of the laboratory local to the participating center decided in each individual case which of the cultured organisms was the causative pathogen.

All isolates were tested for susceptibility to cefdinir and cefuroxime using disk diffusion in agar to determine the zone diameter of complete inhibition of bacterial growth; susceptibility testing was performed in accordance with National Committee for Clinical Laboratory Standards or appropriate local guidelines.[14-16] Isolated pathogens also were subjected to serial dilution minimum inhibitory concentration (MIC) determination for cefdinir, using Sensititre® (Accumed Inc., Westlake, Ohio) microbroth MIC plates containing 12 serial dilutions of cefdinir (range, 0.015–32 mg/L).

The isolated pathogens were tested, if appropriate, for β-lactamase production, using the cefinase disk for *H. influenzae*, *M. catarrhalis*, and *S. aureus*.

Treatment Randomization and Blinding

Each patient was randomized to receive cefdinir 600 mg once a day, 300 mg twice a day, or cefuroxime axetil 250 mg twice a day, for 10 days, the latter being used as an active control in preference to a placebo.

An independent, computer-generated randomization schedule was prepared for each study center. A block size of six patients was used, with three treatment replicates per block, consistent with the proposed 1:1:1 treatment group ratio.

Study medication was provided as identical cefdinir, cefuroxime, or placebo capsules, packaged for each center and pre-labelled with sequential patient numbers, according to the randomization schedule. At each study center, patients who met the entry criteria at screening were given the next consecutive patient number and dispensed the corresponding pre-labelled study medication.

Measurement of Efficacy

Efficacy was assessed at a test-of-cure (TOC) visit between 7 and 14 days post-treatment and a long-term follow-up (LTFU) visit between 21 and 35 days post-treatment. The LTFU assessment provided information on recurrence of infection. The primary measures of efficacy included microbiologic eradication rate by pathogen and clinical response rate.

Microbiologic responses by pathogen at the TOC and LTFU visits were categorized as "eradication" (no baseline pathogen in the follow-up culture or no sputum available for culture, owing to presumed eradication), "persistence" (baseline pathogen present in follow-up culture), or "not assessable."

Clinical assessment of patients included the investigators' evaluations of signs and symptoms, such as cough; sputum production and appearance; dyspnea; rales; rhonchi; fremitus; wheezing; pleural rub; and fever. The clinical response at the TOC visit was categorized as "cure" (absence or satisfactory remission of all baseline signs and symptoms), "failure" (no significant remission of baseline signs and symptoms), or "not assessable." No outcome of "improved" was used. At the LTFU visit, the failure category was replaced by "failure/recurrence" (worsening or no significant remission of baseline signs and symptoms since the previous visit).

A secondary efficacy parameter was the appearance of new pathogens during or after treatment. These were categorized as "superinfection" (appearance of a non-baseline pathogen up to and including the TOC visit and less than 50% clinical improvement, based on a standardized clinical algorithm), "reinfection" (appearance of a new pathogen and classification of recurrence at LTFU) or "not assessable."

The populations that were evaluated for efficacy included the evaluable patient group (those with a baseline pathogen and no major protocol violations likely to affect assessment of efficacy), the intent-to-treat (ITT) group (patients who were randomized to treatment), and at the LTFU visit, the group of qualified patients (evaluable patients who did not have additional protocol violations between TOC and LTFU).

Measurement of Tolerability

Each patient who was randomized to treatment and who received study medication was evaluated for safety. Evaluations of cefdinir and cefuroxime were based on the frequency of adverse events, their intensity, the frequency of treatment discontinuation due to adverse events, and the outcome of physical examinations and clinical laboratory tests.

Adverse events included any concurrent illness or symptom (except those related to chronic bronchitis) reported by the investigators during the study; these complaints were converted to the preferred coding symbols for thesaurus of adverse reaction terms (COSTART).[17]

Statistics

The study was designed with a sample size of 190 evaluable patients per randomized group (n = 3) (1140 patients, if the evaluability rate is 50%). A microbiologic eradication rate of 90% was assumed in the sample-size calculation. The sample size was calculated to provide at least 80% power to assess the equivalence of the cefdinir and cefuroxime microbiologic eradication rates at the TOC visit.

In relation to efficacy, two-tailed 95% confidence intervals (CI) about the difference between response rates (e.g., cefdinir o.d. minus cefuroxime b.i.d.) were calculated, using pooled estimates of treatment group response rates, and compared with a set of fixed criteria. For any two regimens to be equivalent, each 95% confidence interval had to contain 0 and fall within specific boundaries (if the estimated response rate [ERR] was ≥90%, the 95% CI for the difference had to be ±10%; if the ERR was 80–89%, the 95% CI had to be ±15%; and if the ERR was 70–79%, the 95% CI had to be ±20%).

An exploratory Cochran-Mantel-Haenszel (CMH) test was used to compare differences between treatment groups. The Breslow-Day test was employed to evaluate treatment-by-center interaction.

A CMH test, adjusting for center, was performed to compare differences between treatment groups (pairwise) in terms of the rates of drug-related adverse events, diarrhea, and treatment discontinuations due to adverse events.

RESULTS

Patients (n = 1045) in 36 centers were randomized to treatment with cefdinir once a day (n = 349), cefdinir twice a day (n = 347), or cefuroxime twice a day (n = 349). Patients were equally distributed among the treatment groups in terms of age, sex, and prior medical history; however, there were more males than females within each treatment group (Table 1). Most patients were in the age range 18 to 64 years (63%) and approximately one-third (36%) of all patients was aged 65 or over (not shown).

Table 1. Patient Characteristics and Baseline Symptoms

	Intent-to-Treat Group (n = 1045)			*Evaluable Test-of-Cure Group (n = 589)*		
	Cefdinir Once a Day	*Cefdinir Twice a Day*	*Cefuroxime Twice a Day*	*Cefdinir Once a Day*	*Cefdinir Twice a Day*	*Cefuroxime Twice a Day*
Number of patients	349	347	349	201	195	193
Male : female (%)*	64:36	58:42	60:40	62:38	61:39	57:42
Median age (y)	59	59	61	59	59	59
(range, y)	(18–91)	(15–88)	(20–92)	(18–89)	(21–88)	(20–86)
Medical history (%)						
≥1 episode of LRTI within last 12 months	63	70	72	—	—	—

*Percentages are rounded and may not add up to 100%. LRTI = lower respiratory tract infection.

Over 95% of enrolled patients had a moderate or severe cough at baseline, and over 90% had moderate or severe sputum production. Most patients also had rhonchi (71%) and wheezing (52%), and almost half had moderate or severe dyspnea (49%). Approximately one-third of patients presented with rales, 20% with fever, and less than 10% with fremitus or pleural rub. Similar numbers of patients had experienced lower respiratory tract infections (LRTIs) in the year preceding the study (see Table 1). In each treatment group, 34% of patients were past smokers and between 28% and 32% were current smokers.

In 752 of 1045 patients (72%), 882 pathogens were isolated at baseline and multiple pathogens were cultured from 115 patients (11%). The most common pathogens were *H. influenzae*, *S. pneumoniae*, *H. parainfluenzae*, and *S. aureus*. Over 94% of pathogens tested were susceptible to both study drugs (Table 2). The number of pathogens resistant to cefdinir and cefuroxime was 36 of 867 (4%) and 28 of 863 (3%), respectively (see Table 2).

Thirty-one isolates of *S. pneumoniae* were tested for penicillin susceptibility at baseline, all were susceptible to penicillin. All but one of these isolates were tested for cefdinir and cefuroxime susceptibility and all 30 were found to be susceptible to both drugs.

Among all patients treated, 940 (90%) completed a median of 10 days of treatment with study medication, with no differences among the three regimens. At the TOC visit, 456 patients were unevaluable mainly owing to absence of a baseline pathogen. Thus, 589 patients were included in the evaluable patient population. A further 173 patients were disqualified from the analyses at the LTFU visit, mainly owing to missing cultures or no clinical assessment, leaving 416 patients in the qualified group.

Efficacy

Test-of-Cure Assessment

In the evaluable group, the microbiologic eradication rates by pathogen were 90% in the cefdinir once a day group, 85% in the cefdinir twice a day group, and 88% in the cefuroxime twice a day group (Table 3; Figure 1). The 95% confidence interval for the comparison of eradication rates by pathogen indicated that cefdinir once a day and cefdinir twice a day were comparable to cefuroxime twice a day, but that cefdinir once a day was slightly more effective than cefdinir twice a day (see Figure 1).

The clinical response rates with cefdinir once a day, cefdinir twice a day, and cefuroxime twice a day were 81%, 74%, and 80%, respectively (see Figure 1). The 95% confidence interval for the comparisons of clinical response showed that there were no differences among the three regimens.

The exploratory CMH tests showed no significant differences between the drugs on any efficacy parameter at the TOC visit.

Clinical cure rates in patients 65 years of age and older were similar to those in younger adults in all treatment groups (Table 4). Smoking history did not appear to affect successful clinical outcomes, except among

Table 2. Pathogen Susceptibility to Treatment at Baseline

	Cefdinir				*Cefuroxime*			
Pathogen (n = 882)	*S (n = 798)*	*I (n = 33)*	*R (n = 36)*	*U (n = 15)*	*S (n = 752)*	*I (n = 83)*	*R (n = 28)*	*U (n = 19)*
Gram-positive								
Streptococcus pneumoniae (n = 137)	132	0	4	1	132	2	1	2
Staphylococcus aureus (n = 74)	69	0	3	2	68	2	1	3
Streptococcus pyogenes (n = 17)	17	0	0	0	15	2	0	0
Other (n = 8)	8	0	0	0	6	2	0	0
Gram-negative								
Haemophilus influenzae								
β-lactamase + (n = 29)	29	0	0	0	28	1	0	0
β-lactamase – (n = 243)	218	19	3	3	233	3	4	3
β-lactamase unknown (n = 5)	5	0	0	0	5	0	0	0
Haemophilus parainfluenzae								
β-lactamase + (n = 10)	8	1	1	0	10	0	0	0
β-lactamase – (n = 63)	56	4	1	2	61	2	0	0
β-lactamase unknown (n = 12)	10	0	2	0	12	0	0	0
Moraxella catarrhalis								
β-lactamase + (n = 37)	37	0	0	0	34	3	0	0
β-lactamase – (n = 37)	35	2	0	0	33	3	0	1
β-lactamase unknown (n = 2)	0	0	0	2	0	0	0	2
Escherichia coli (n = 52)	49	0	2	1	32	18	0	2
Klebsiella pneumoniae (n = 30)	30	0	0	0	22	8	0	0
Other (n = 126)	95	7	20	4	61	37	22	6

S = susceptible (MIC < 0.06 mg/L); I = intermediate susceptibility (MIC 0.1–1.0 mg/L); R = resistance (MIC > 2.0 mg/L); U = unknown; + = positive; – = negative.

Table 3. Microbiologic Eradication Rate by Pathogen at Test-of-Cure and Long-Term Follow-up Examinations

	Number of Pathogens					
	At Test-of-Cure Visit (n = 666)			*At Long-Term Follow-up Visit (n = 430)*		
Pathogen	*Cefdinir o.d. 199/221 (98.0%)*	*Cefdinir b.i.d. 192/225 (85.3%)*	*Cefuroxime b.i.d. 193/220 (87.7%)*	*Cefdinir o.d. 144/152 (94.7%)*	*Cefdinir b.i.d. 134/136 (98.5%)*	*Cefuroxime b.i.d. 140/142 (98.6%)*
Gram-positive						
S. aureus	16/16	19/20	23/23	10/10	10/11	18/18
S. pneumoniae	34/38	35/40	30/30	23/27	27/27	21/21
S. pyogenes	4/4	4/5	4/4	3/3	3/3	1/1
Other	0/0	3/3	2/2	0/0	0/0	2/2
Gram-negative						
H. influenzae						
β-lactamase +	4/4	4/7	8/10	–	–	–
β-lactamase –	51/65	53/66	43/60	–	–	–
β-lactamase unknown	1/1	1/1	1/1	38/42*	40/40*	38/39*
H. parainfluenzae						
β-lactamase +	2/2	3/3	3/3	–	–	–
β-lactamase –	13/13	21/24	15/16	–	–	–
β-lactamase unknown	4/4	3/3	2/2	13/13*	19/19*	13/13*
M. catarrhalis						
β-lactamase +	14/14	4/6	8/9	–	–	–
β-lactamase –	5/5	13/14	12/12	–	–	–
β-lactamase unknown	–	–	–	15/15*	11/11*	14/14*
E. coli	10/12	7/9	13/16	8/8	5/6	13/13
K. pneumoniae	12/12	6/8	3/3	8/8	3/3	3/3
Other	29/31	16/16	26/29	26/26	16/16	17/18

+ = positive; – = negative. *Combined β-lactamase categories.

cefuroxime-treated patients, in whom clinical cure rates were slightly higher among patients who had never smoked.

In the ITT population, analyses of the 95% confidence interval for microbiologic eradication rates by pathogen and by patient, and the clinical response by patient, confirmed that cefdinir once a day, cefdinir twice a day, and cefuroxime twice a day had comparable efficacy.

Long-Term Follow-up Assessment

At LTFU assessment, the three regimens were comparable as judged by the three primary measures of efficacy (see Table 3 and Figure 1). The microbiologic eradication rates by pathogen were 95% with cefdinir once a day, 99% with cefdinir twice a day, and 99% with cefuroxime twice a day. The corresponding values for clinical response by patient were 93%, 95%, and 93%, respectively (see Figure 1).

The analysis of data from the ITT population at the LTFU visit showed that all three treatment groups had comparable responses.

During the study, 116 patients developed a respiratory tract superinfection: 32 patients in the cefdinir once a day group, 45 in the cefdinir twice a day group, and 39 in the cefuroxime twice a day group. Eleven patients were reinfected after the TOC visit with pathogens not present at baseline: three patients in the cefdinir once a day group, six patients in the cefdinir twice a day group, and two in the cefuroxime twice a day group.

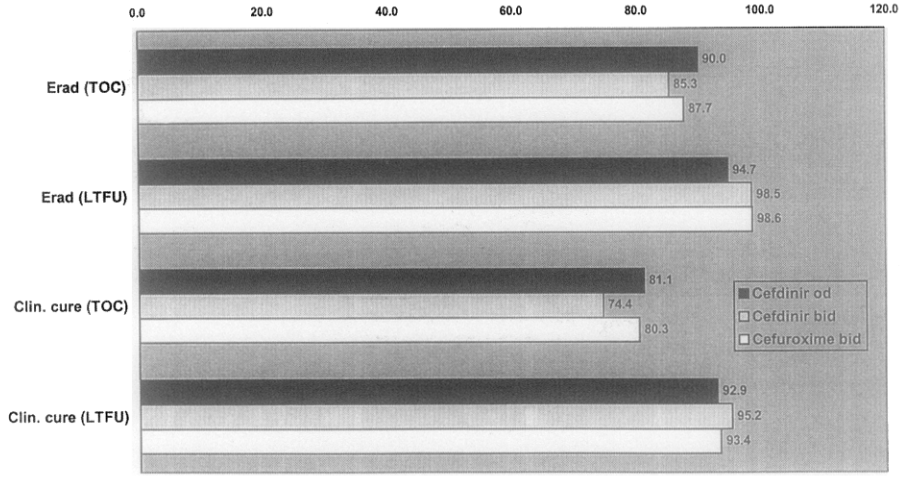
Tolerability

Two patients who were randomized to treatment did not receive study medication. Thus, 1043 were evaluated for safety: 349 receiving cefdinir once a day, 345 receiving cefdinir twice a day, and 349 receiving cefuroxime twice a day (see Table 4).

Overall, adverse event rates during therapy were similar in each group. Drug-related adverse events were observed in 50 of 349 patients (14%) with cefdinir once a day, 44 of 345 (13%) with cefdinir twice a day, and 39 of 349 (11%) with cefuroxime twice a day. There were no statistically significant differences among the regimens. Most adverse events occurred within the first 5 days of treatment and were mild or moderate in intensity.

The majority of complaints related to the digestive system. Diarrhea was the most frequent drug-related adverse event, occurring in 29 patients (8.3%) receiving cefdinir once a day, 27 (7.8%) receiving cefdinir twice a day, and 19 (5.4%) receiving cefuroxime twice a day, followed by nausea in seven (2%), three (0.9%), and eight patients (2.3%), respectively. Other adverse events occurred with a frequency of less than 2%.

Severe gastrointestinal hemorrhage occurred in one patient after 4 days of treatment with cefuroxime twice a day. This was the only serious adverse event that was considered possibly related to treatment. Thirty-four patients discontinued treatment because of adverse events that were considered related to treatment (15 in the cefdinir o.d. group, 10 in the cefdinir b.i.d. group,



	95% CI	*Fixed Criteria (%)*	*Result*
Microbiologic eradication rate by pathogen			
Cefdinir o.d.–cefuroxime b.i.d	−3.5, 8.2	± 10	Equivalent
Cefdinir b.i.d.–cefuroxime b.i.d.	−8.7, 3.9	± 15	Equivalent
Cefdinir o.d.–cefdinir b.i.d.	−1.4, 10.8	± 10	Not equivalent
Clinical response rate			
Cefdinir o.d.–cefuroxime b.i.d	−7.0, 8.6	± 15	Equivalent
Cefdinir b.i.d.–cefuroxime b.i.d.	−14.3, 2.4	± 15	Equivalent
Cefdinir o.d.–cefdinir b.i.d.	−1.4, 14.9	± 15	Equivalent

Analyses based on pooled rates at the test-of-cure visit.

Figure 1. Graphic illustration of overall treatment response (*top*); table presenting 95% confidence interval for comparison of eradication rates and clinical response rates (analyses based on pooled rates at test-of-cure) (*bottom*). Erad = eradication rate; TOC = test-of-cure; LTFU = long-term follow-up; clin. cure = clinical response.

and 9 in the cefuroxime b.i.d. group), the most frequent reason being diarrhea. Pairwise comparisons showed no differences in discontinuation rates among the treatment groups. Rash caused discontinuation in 1% of each cefdinir group and in 0% of the cefuroxime-treated patients. No clinically important adverse events were noted during physical examinations or clinical laboratory tests.

DISCUSSION

This was a large, multicenter, double-blind study designed to evaluate the efficacy and safety of two dosages of cefdinir versus cefuroxime in the treatment of patients with AECB. The study group comprised 1045 patients who were randomized to receive either cefdinir or cefuroxime. The results indicate that the efficacy and tolerability of cefdinir and cefuroxime were comparable with no significant differences among the regimens used.

In the test population, patients had to have AECB of presumptive bacterial origin. Nonbacterial respiratory pathogens (e.g., mycoplasma, chlamydia, legionella, influenza, and other viral causes) were not assessed. It was found that the bacterial pathogens responsible for AECB in this study were typical of those associated with AECB, and they responded well to cefdinir and cefuroxime. Nevertheless, the exact role of bacterial and viral infection in AECB has been disputed; bacterial colonization has been found during remission periods as well as during acute exacerbations.[18] There is a lack of clear data identifying patients who might benefit from antibiotic treatment, although some believe that antibiotics should be reserved for those with pneumonia.[18]

In this study, AECB responded comparably to the two antibiotics. At the TOC assessment, the 95% confidence interval for the comparison of eradication rates by pathogen and the clinical response rate by patient indicated that cefdinir once a day and twice a day were

Table 4. Clinical Cure Rates at Test-of-Cure by Patient Age and Smoking History among Evaluable Patients

	Cefdinir o.d. n (%)	*Cefdinir b.i.d. n (%)*	*Cefuroxime b.i.d. n (%)*
Patient age (y)			
18–64	100/129 (77.5)	98/134 (73.1)	102/122 (83.6)
≥65	63/72 (87.5)	47/61 (77.0)	53/71 (74.6)
Smoking history			
Current smoker	48/60 (80.0)	42/60 (70.0)	50/60 (83.3)
Past smoker	56/70 (80.0)	55/72 (76.4)	46/69 (66.7)
Never smoked	59/71 (83.1)	48/63 (76.2)	59/64 (92.2)

Table 5. Summary of Drug-Related Adverse Events

	Cefdinir o.d.	*Cefdinir b.i.d.*	*Cefuroxime b.i.d.*
Number of patients	349	345	349
Drug-related adverse events by body system (n)	50	44	39
Digestive system	37	36	31
Diarrhea	29	27	19
Nausea	7	3	8
Skin and appendages	9	6	1
Body as a whole	7	4	7
Urogenital system	3	1	1
Special senses	1	1	2
Nervous system	1	0	1
Metabolic or nutritional	0	1	0
Blood and lymphatic systems	0	0	0
Musculoskeletal	0	0	0
Cardiovascular system	0	0	0
Respiratory system	0	0	0
Intensity of drug-related events (%)*			
Mild	8.9	7.2	8.0
Moderate	6.0	5.2	2.3
Severe	1.1	0.3	1.1
Treatment discontinuation owing to drug-related adverse events n (%)	15 (4.3)	10 (2.9)	9 (2.6)

*Percentage of patients with multiple adverse events counted once in each applicable category. A patient could have more than one adverse event per body system.

equivalent to cefuroxime twice a day. Overall, the clinical response rates were somewhat lower than the microbiologic response rates (74–81% vs. 85–90%), which may be attributable to underlying viral infections that also can cause AECB.[2] Furthermore, the responses to cefdinir twice a day were slightly lower than those with cefdinir once a day and cefuroxime twice a day (74–85% vs. 80–90%). However, an exploratory CMH test showed no significant differences among the regimens on any efficacy parameter at this visit.

Similar relapse rates were seen in patients receiving cefdinir and cefuroxime. At the LTFU assessment, all three drug regimens were comparable in patients who had eradication at the TOC visit, as judged by the primary efficacy measures. These findings indicated that cefdinir and cefuroxime continued to provide good response in those patients in whom treatment initially was successful.

In a randomized, double-blind, crossover comparison of broad-spectrum antibiotic and placebo therapy in 173 patients with exacerbation of chronic obstructive pulmonary disease (COPD), the success rate was 55% with placebo and 68% with either trimethoprim-sulphamethoxazole, amoxicillin, or doxycycline.[19] The difference between antibiotic and placebo was greatest in patients with type 1 exacerbation (the occurrence of increased dyspnea, sputum volume, and sputum purulence).[19] The present study did not stratify patients by exacerbation type, because pre-exacerbation rates were not available; in addition, the sample sizes became too small for effective analysis and statistical testing. However, most of the patients in the study could be categorized as those having type 1 exacerbation, in whom, according to the work of Anthonisen et al,[19] one would expect a "large advantage for antibiotic therapy." In support of antibiotic use in AECB, a meta-analysis of randomized trials has indicated that there was a small but statistically significant improvement attributable to antibiotic therapy in patients with exacerbation of COPD that may be clinically significant in those with low baseline flow rates.[20]

Although there were no patients with known penicillin-resistant isolates of *S. pneumoniae*, three cefdinir-treated patients were noted to have cefdinir-resistant strains of *S. pneumoniae*. In each case, the category of clinical response at TOC was cure; one patient had microbiologic persistence at TOC, whereas the other two had eradication. The investigators also identified 20 *H. influenzae* isolates that were β-lactamase-negative and amoxicillin-resistant. At the short-term follow-up, the clinical and microbiologic responses of 12 of these isolates were categorized as cure and eradication, and with four isolates the responses were categorized as cure and persistence, respectively. These findings suggest that cefdinir is effective against pathogens that are resistant to standard agents.

Although this study did not specifically consider causative factors associated with AECB, it may be relevant that approximately one-third of patients were past smokers, about the same proportion were currently smoking, and one-third were elderly (over 65 years). In the cohort investigated by Anthonisen and colleagues,[19] 94% of the patients had a history of smoking, with 21% still smoking at the time of enrollment; the average age of their patients was 67 years.

Cefdinir and cefuroxime were equally well tolerated with no significant differences among regimens. Most adverse events occurred in the first 5 days of treatment

and were mild or moderate in intensity. Diarrhea was the most frequent drug-related complaint with both drugs. There were no significant differences between cefdinir and cefuroxime in terms of discontinuations owing to adverse events. Indeed, the safety profile of cefdinir was similar to that of cefuroxime and other cephalosporins used for LRTIs, including AECB.[3,4,21-23]

CONCLUSIONS

Cefdinir 600 mg once a day was as effective as cefuroxime 250 mg twice a day in terms of microbiologic response by pathogen and clinical response in patients with AECB of presumptive bacterial origin. Cefdinir 300 mg twice a day was as effective as cefuroxime twice a day in terms of microbiologic response by patient. All three treatments were well tolerated with no significant differences among regimens in terms of frequency of adverse events or numbers of patients discontinuing treatment because of adverse events.

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