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Randomized Comparative Study of Cefixime versus Cephalexin in Acute Bacterial Exacerbations of Chronic Bronchitis

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Patients with purulent exacerbation of chronic bronchitis were randomized to receive either a single 400-mg daily dose of cefixime or 250 mg of cephalexin, orally, four times a day. Patients were males with a mean age of 63 years. Of the 86 patients, 71 (82%) had bronchitis caused by a single organism (29 by *Haemophilus influenzae*, 27 by *Branhamella catarrhalis*, 9 by gram-negative enteric organisms, 6 by *Streptococcus pneumoniae*), while more than one pathogen was implicated in 15 patients (18%). A total of 70.8% of the cefixime group and 50% of the cephalexin group were clinically cured ($\chi^2 = 3.89$, $P < 0.05$); however, when the categories of cured and improved were combined, no significant difference was noted between treatment groups ($\chi^2 = 3.39$, $P = 0.06$). Analysis of side effects included all 130 evaluable and nonevaluable patients: diarrhea was noted in six patients in the cefixime group and none of the patients in the cephalexin group ($P = 0.013$ by the Fisher exact test). The diarrhea was mild and self-limited in all cases. *B. catarrhalis* has emerged as a major cause of exacerbation of bronchitis in our experience; there is an increased need to emphasize the examination of sputum samples by Gram staining if cost-effective antibiotic choices are to be made; any empirically chosen antibiotic should have activity against β-lactamase-producing strains of *B. catarrhalis* as well as *S. pneumoniae* and *H. influenzae*.

In a population of patients with chronic bronchitis, acute bacterial exacerbations of bronchitis are frequently seen (4). Such exacerbations often cause worsening of other comorbid conditions and contribute to hospitalization and indirectly to death. Although there has been debate about the need for and the efficacy of antimicrobial therapy in this setting (2, 10, 18), most physicians continue to treat well-documented bacterial exacerbations of chronic bronchitis.

In the present study we compared the effects of a newer oral cephalosporin, cefixime, against those of cephalexin in the treatment of acute bacterial bronchitis. Cefixime is a β-lactamase-stable cephalosporin that, because of its in vitro activity against gram-negative enteric pathogens, is considered the first broad-spectrum oral cephalosporin (19). It has a sufficiently long half-life (4 h) to allow for once-daily dosing, and the peak level in serum after a 400-mg dose is 3 to 5 μg/ml (7). Cefixime has excellent in vitro activity against pathogens considered important in patients with bronchitis, including β-lactamase-producing *Branhamella catarrhalis* and *Haemophilus influenzae* (MIC for 90% of strains [MIC_{90}], 0.25 μg/ml for both organisms) and *Streptococcus pneumoniae* (MIC_{90}, 0.2 μg/ml) (3).

Cephalexin, the comparative agent, is often selected by clinicians in the empiric treatment of patients with acute bronchitis. It is active against *S. pneumoniae* (MIC_{90}, 3.1 μg/ml), *B. catarrhalis* (MIC_{90}, 0.5 μg/ml), and β-lactamase-negative *H. influenzae* (MIC_{90}, 6.0 μg/ml) (9) and is generally well tolerated. A mean peak level of 10 μg/ml in serum is typical after a single 250-mg dose of cephalexin (12). The β-lactamase enzymes of *B. catarrhalis* are unique in that they do not hydrolyze cepahlexin as rapidly as ampicillin or cefaclor does (20). Although β-lactamase positive *H. influenzae* represent a major void in the spectrum of cephalexin, less than 5% of our *H. influenzae* isolates in prior years produced β-lactamase.

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MATERIALS AND METHODS

Study patients. Patients were recruited from the Johnson City Veterans Administration Medical Center domiciliary clinic, emergency room, and acute-care wards. Acute bacterial exacerbation of chromic bronchitis was defined by using the modified clinical and laboratory criteria described by Chodosh (4). Clinical criteria included increasing cough, increased sputum volume, and increasing dyspnea. Laboratory criteria included a Gram stain showing less than 10 epithelial cells on low power and greater than 25 polymorphonuclear neutrophils, with bacteria (of one or more types) being readily visible on high-power examination. Culture confirmation of a pathogen was required for evaluability. Patients were excluded from entry into the study if they had a known penicillin allergy, if they had received antibiotic therapy in the 3 days prior to enrollment in the study, or if a new pulmonary infiltrate was noted on chest radiograph.

Treatment procedures and evaluation. The study was reviewed and approved by the Institutional Review Board, East Tennessee State University, and the Research and Development Committee, Johnson City Veterans Administration Medical Center. After informed consent was obtained, patients were randomized to receive cefixime at 400 mg daily or cephalexin at 250 mg every 6 h for 14 days. At the time of entry into the study, base-line data (see Table 1) were obtained for each patient and a sputum sample was cultured by standard methods. Susceptibility to cefixime and cephalexin was determined by determining the zone diameter of inhibition as well as by MIC testing by using the Sensititre system (GIBCO Laboratories, Lawrence, Mass.). Testing for β-lactamase production was performed by the chromogenic cephalosporin assay (Cefinase; BBL Microbiology Systems, Cockeysville, Md.).

Patients were seen 3 to 5 days after enrollment into the study for assessment of symptoms and to obtain a follow-up sputum sample for culture, if one could be produced. Patients were also seen at the conclusion of therapy, and a

TABLE 1. Comparison of treatment groups

Variable	Cephalexin (n = 38)	Cefixime (n = 48)	Statistical test
Age (yr)	62.5 ± 11.1	63.38 ± 9.7	t = 0.36 (NS[a])
Duration (days)[b]	3.0 ± 1.7	2.92 ± 1.6	t = 0.23 (NS)
Wt (lb [kg])	165.9 ± 43.4 (75.3 ± 19.7)	159.6 ± 34.6 (72.4 ± 15.6)	t = 0.74 (NS)
Temp (°F [°C])	98.0 ± 1.0 (36.7 ± 0.3)	97.9 ± 1.4 (36.6 ± 0.5)	t = 0.07 (NS)
Systolic blood pressure (mm Hg)	124.6 ± 20.0	125.5 ± 18.7	t = 0.20 (NS)
Diastolic blood pressure (mm Hg)	76.5 ± 10.7	75.5 ± 11.4	t = 0.39 (NS)
Respiration rate (breaths/min)	20.1 ± 2.4	19.8 ± 3.0	t = 0.63 (NS)
Hemoglobin (g/dl)	14.3 ± 1.7	14.5 ± 1.7	t = 0.59 (NS)
Leukocytes (10^3/mm^3)	10.9 ± 3.0	10.5 ± 3.4	t = 0.56 (NS)
Creatinine (mg/dl)	1.2 ± 0.4	1.2 ± 0.4	t = 0.35 (NS)
COPD (no. [%])[c]	28 (74)	34 (71)	χ^2 = 0.08 (NS)
ASHD (no. [%])[d]	24 (63)	18 (37)	χ^2 = 5.5 (P = 0.02)
Corticosteroid use	9 (23)	6 (12)	χ^2 = 1.84 (NS)

[a] NS, Not statistically significant.
[b] Duration of symptoms of exacerbation of bronchitis prior to enrollment in study.
[c] COPD, Chronic obstructive lung disease.
[d] ASHD, Atherosclerotic heart disease, as evidenced by history of myocardial infarction, angina, or heart failure.

sputum sample, if available, was cultured. Patient compliance and final drug accountability were assessed by tablet counts and interviews. Patients were questioned about possible adverse reactions on each visit. Patients who had to discontinue either medication were monitored for 1 week or until the resolution of their symptoms.

The clinical response was defined as (i) cure, in which symptoms abated completely and there was no evidence of fever or sputum production at follow-up; (ii) improvement, in which symptoms were substantially alleviated but with incomplete resolution of evidence of infection; or (iii) failure or relapse, in which there was no response to therapy or there was clinical improvement followed by deterioration during or after treatment.

Exclusions after start of treatment. Of the 130 patients enrolled in the study, 44 were excluded after treatment had begun. The major reason for exclusion was due to failure to recover a pathogen on culture (23 patients). Others were excluded on the basis of lack of susceptibility data (nine patients), loss to follow-up (five patients), inadvertant removal from the study (four patients), and recovery of a resistant pathogen (three patients).

Data analysis. Patients were judged to be evaluable for data analysis if they had received the study drug for at least 7 days, unless they had a clear-cut failure of clinical response prior to that time. For evaluable patients, the mean base-line values of continuous variables of the two medication groups were compared by using the two-tailed t test for independent samples, and the contingency table χ^2 test was used to compare group proportions (see Table 1). Clinical outcomes among patient subgroups defined by pathogen or treatment were compared by using χ^2 contingency table analysis. Differences in medical and epidemiological characteristics of pathogen-defined groups were compared by the χ^2 contingency table test or the Fisher exact probability calculation procedure for categorical variables and analysis of variance for continuous variables. Side effects in all patients enrolled in the study were evaluated. Probability levels of 0.05 or smaller were used to indicate statistical significance.

RESULTS

Comparison of treatment groups. Of 86 evaluable patients, 38 received cephalexin and 48 received cefixime. The two treatment groups were comparable for all factors included in Table 1, with the exception of atherosclerotic heart disease, which was found more frequently in the cephalexin group (63 versus 37%; P = 0.02).

Etiologic agents. The two leading causes of acute bacterial exacerbation of chronic bronchitis were *H. influenzae* and *B. catarrhalis*, accounting for over 60% of cases (Fig. 1). The third largest category was a mixed group in which more than one pathogen was recovered (Fig. 2); *B. catarrhalis* and *H. influenzae* were also predominant in this mixed group. Overall, 37% of all *B. catarrhalis* isolates and 14% of all *H. influenzae* isolates produced β-lactamase.

Response to therapy. There were 70.8% cures in the group treated with cefixime compared with 50% cures in the group treated with cephalexin ($P < 0.05$) (Table 2). However, when the categories of cured and improved were combined, no significant difference was noted between treatment groups (95.8% for cefixime versus 84.2% for cephalexin; P = 0.06).

Side effects of therapy. For analysis of side effects, all 130 evaluable and nonevaluable patients who received either drug for any period of time were included. Twelve patients who received cefixime and three patients who received cephalexin reported side effects (Table 3). These episodes were usually mild and were not always clearly related to the study drug, as many patients were receiving other medications. Six patients in the group treated with cefixime and no patients in the group treated with cephalexin experienced diarrhea (P = 0.013, Fisher exact test). While the diarrhea was mild in all instances, one patient requested to be removed from the study for this symptom.

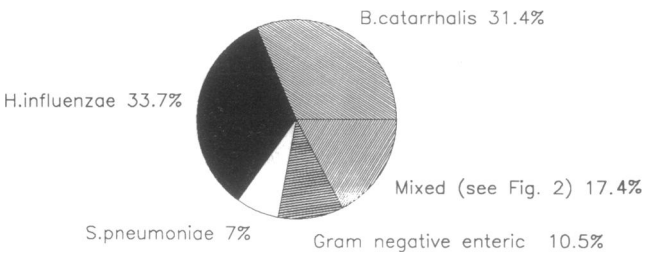

FIG. 1. Etiologic agents of bacterial exacerbation of chronic bronchitis (86 patients).

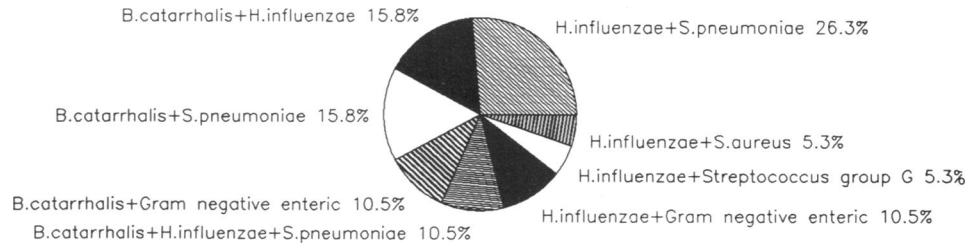

FIG. 2. Types of mixed bacterial exacerbation of chronic bronchitis (15 patients).

DISCUSSION

Many physicians who treat adult patients with chronic bronchitis agree that acute exacerbations of illness do occur and that these episodes are characterized by worsening cough; increased production of purulent sputum; and on occasion, fever, malaise, and shortness of breath. A bacterial etiology for these episodes is frequently suspected; and pathogens such as *H. influenzae*, *B. catarrhalis*, and *S. pneumoniae* have been implicated. A Gram stain of sputum samples that shows that the samples are relatively free of oral contamination and that there are bacterial organisms visible in high numbers along with a confirmatory culture is the most common method of determining a bacterial causation of these exacerbations. While other techniques such as transtracheal aspiration or sheathed bronchoscopy allow more definitive proof of bacterial causation, they are difficult to apply routinely in an outpatient setting. Chodosh (4) has shown that antibiotic therapy is effective in reducing clinical symptoms and decreasing the indices for inflammation on Gram staining of sputum samples in a patient population with acute infectious exacerbations of chronic bronchitis. In view of data such as these, clinicians often initiate empiric antibiotic therapy when dealing with patients in this setting.

When choosing an antimicrobial agent for empiric use, the prescribing physician should consider several factors, including the expected microbiology at the site of infection; the antibacterial spectrum associated with the possible agents of choice; and potential side effects, ease of administration, and cost of the possible agents. With regard to the microbiology associated with acute exacerbation of chronic bronchitis, it is noteworthy that in our population, *B. catarrhalis* was recovered as the predominant pathogen nearly as often as *H. influenzae* was (31.4 versus 33.7%, respectively). Furthermore, it was the most common organism recovered from patients with multiple (mixed) pathogens isolated from sputum culture. This is a particularly important finding since 37% of our *B. catarrhalis* isolates produced β-lactamase and drugs such as ampicillin or amoxicillin, which are often selected in the empiric treatment of respiratory tract infections, would be ineffective against such organisms. The 37% incidence of β-lactamase production by our *B. catarrhalis* isolates was lower than expected: a previous study by Alvarez et al. (1) of 53 clinical isolates of *B. catarrhalis* from the Veterans Administration Medical Center revealed that 87% produced β-lactamase. Wallace et al. (20) have elegantly shown that β-lactamase production by strains of *B. catarrhalis* in the United States is a recent event, probably occurring around 1976; 18 strains recovered between 1952 and 1975 were all enzyme negative. By 1983 the prevalence of β-lactamase-producing strains at the University of Texas Health Center had already reached 75%.

The significance of *B. catarrhalis* as a respiratory pathogen, particularly in patients with underlying pulmonary disease (8, 14), and its susceptibility to antimicrobial agents (15, 17) have been reported previously. However, our data are in contrast to the findings of other investigators, who either failed to recover *B. catarrhalis* (5, 6, 13) or noted it to be a less frequent pathogen (10, 11, 16) in patients with chronic lung disease. Thus, the selection of an antimicrobial agent for treatment of an acute exacerbation of chronic bronchitis might preferably include a drug that is resistant to the effects of β-lactamase and that includes the currently recognized significant pathogens (*H. influenzae*, *B. catarrhalis*, and *S. pneumoniae*) in its spectrum.

In the present study, we compared the effects of cefixime and cephalexin in the treatment of patients with acute exacerbation of chronic bronchitis. Cefixime is a new orally administered cephalosporin which, because of its extremely broad spectrum of activity against a variety of aerobic gram-negative bacilli, as well as its β-lactamase stability, is

TABLE 2. Clinical outcomes in the two treatment groups

Organism	No. of patients with indicated clinical outcome[a]								
	Cephalexin			Cefixime			All patients		
	C	I	F	C	I	F	C	I	F
B. catarrhalis	4	4	3	11	4	1	15	8	4
H. influenzae[b]	8	3	1	11	5	1	19	8	2
Gram-negative rods	3	2	0	4	0	0	7	2	0
S. pneumoniae	1	1	2	2	0	0	3	1	2
Mixed	3	3	0	6	3	0	9	6	0

[a] C, Cured; I, improved; F, failed.

[b] One patient in the group treated with cephalexin and three patients in the group treated with cefixime had β-lactamase-producing *H. influenzae*; all patients were either cured or improved.

TABLE 3. Side effects of antibiotic treatment in 130 patients enrolled in the study

Side effect	Cephalexin (n = 65)[a]	Cefixime (n = 65)[a]	Total no.
Nausea	A, B, C	D, E, F, G, H	8
Gas		I	1
Weakness	J	K[b]	2
Vomiting		G, H	2
Rash		L	1
Diarrhea		M, N, O, P[b], Q, G	6[c]
Serum glutamic oxalacetic transaminase rise		E	1
Serum glutamic pyruvic transaminase rise		E	1
Alkaline phosphatase rise	R	H	2

[a] Letters represent individual patients; e.g., patient E had nausea and serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase rises.

[b] Medication was discontinued because of side effects.

[c] P = 0.013 by the Fisher exact test.

thought of as the first broad-spectrum oral cephalosporin (19). Cephalexin, a commonly used antibiotic in the treatment of patients with respiratory tract infections, is resistant to the effects of β-lactamase produced by *B. catarrhalis* and has activity against other major respiratory tract pathogens, including *S. pneumoniae* and non-β-lactamase-producing strains of *H. influenzae*. A total of 130 patients were enrolled in the study, and 86 (48 treated with cefixime and 38 treated with cephalexin) were evaluable according to study criteria. While our two study groups were found to be comparable in most respects (Table 1), it should be noted that our patients represent an elderly male veteran population in which tobacco abuse and chronic lung disorders are frequently described. With regard to clinical outcome (Table 2), cefixime more often resulted in cure (complete clinical improvement) when it was compared with cephalexin. The greater prevalence of atherosclerotic heart disease in the group treated with cephalexin was unexpected and could perhaps account for the differences in clinical outcome. However, when the categories of cure and improved were combined, no statistically significant difference was noted between the study groups. Finally, although cefixime was easily administered in a once-daily dosage, the occurrence of drug side effects (Table 3) was somewhat more common in the group treated with cefixime when compared with that in the group treated with cephalexin (19 versus 5 episodes, respectively). Diarrhea (mild) occurred exclusively in the group treated with cefixime (9.2% of treatment courses) and was the reason for drug discontinuation in one patient.

Overall, cefixime proved to be a very effective and easily administered antimicrobial agent in our population of patients with acute exacerbation of chronic bronchitis. Our microbiological data are impressive because of the frequent recovery of *B. catarrhalis*, 37% of which were β-lactamase producers. Empiric antimicrobial therapy for these lower respiratory tract infections in our setting calls for the use of an appropriate β-lactamase-stable agent.

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