Comparison of Cefadroxil and Cephalexin in the Treatment of Community-Acquired Pneumonia

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Thirty-four patients with community-acquired acute pneumonias were treated in a prospective, randomized trial with either cefadroxil, 500 mg twice daily, or cephalexin, 250 mg four times daily. In both groups of patients, the presence of chronic illnesses predisposing to pneumonia was common. Streptococcus pneumoniae was isolated from 65% of the initial sputum specimens, and most illnesses were of mild to moderate severity. All 19 cases treated with cefadroxil and all 15 cases treated with cephalexin were clinically cured, and adverse reactions to the medications were minimal. The success of these regimens suggests that outpatient use of oral cephalosporin therapy may be an appropriate treatment of patients with mild or moderate community-acquired pneumonia.

Despite advances in health care, pneumonia caused by bacterial pathogens remains a significant problem. In the United States there are an estimated 0.5 to 1.0 million episodes and 50,000 deaths due to pneumonia annually (5, 7). These infections present with varying severity depending on the pathogen, extent of pulmonary involvement, and the age and health status of the host (19). Many patients with bacterial pneumonia do not require hospitalization.

Cephalosporin antibiotics are effective in vitro against several of the most important pathogens causing pneumonia, including Streptococcus pneumoniae, Staphylococcus aureus, Streptococcus pyogenes, Haemophilus influenzae, Klebsiella pneumoniae, and the anaerobic flora of the upper respiratory tract (15). Since community-acquired bacterial pneumonias are commonly due to a wide spectrum of pathogens (6), treatment of such patients with cephalosporins could be appropriate, particularly if broad coverage is desirable because of underlying disease (16) and sputum Gram stain shows no predominant pathogen (4) or sputum examination is not readily available. Newer oral cephalosporin agents permit outpatient treatment of pneumonias of moderate severity, sparing the patient the expense and possible morbidity associated with hospitalization.

Cephalexin has been shown to be an effective oral agent for treatment of community-acquired pneumonia; however, because of its short half-life it must be taken every 6 h (18). Recently, a new oral cephalosporin, cefadroxil, has been introduced which has a similar spectrum of biological activity to cephalexin (12) but, because of a longer serum half-life, needs to be administered only every 12 h (9). We believed that cefadroxil would simplify the outpatient management of pneumonia in selected patients, because of the halving of the dosage schedule. Therefore, we began a prospective, randomized, observer-blind study of the efficacy of oral cephalaxin and cefadroxil in moderately ill patients diagnosed as having community-acquired pneumonia.

MATERIALS AND METHODS

Patients. From October 1981 through June 1982, patients evaluated for possible pneumonia by the medical services of the Denver Veterans Administration Medical Center (DVAMC) and the LDS Hospital (LDSH) were considered for the study. Patients were asked to enroll in the study if they had a clinical history compatible with acute onset of pneumonia, chest roentgenogram showing a new infiltrate, and a sputum Gram stain showing less than 10 epithelial cells per oil immersion field, numerous polymorphonuclear leukocytes, and predominantly gram-positive flora. Informed consent was obtained in each instance. Excluded from the study were pregnant women, children, and patients with the following conditions: history of hypersensitivity to beta-lactam antibiotics, inability to take or absorb oral medication, chronic renal or hepatic failure, granulocytopenia, rapidly progressive pneumonia necessitating parenteral therapy, or history of having received other antibiotics in the prior 72 h.

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Microbiological studies. Cultures of sputum were obtained from all patients, and cultures of blood were obtained from all but two patients (one in each treatment group) before antimicrobial therapy was begun. Cultures were performed at the end of treatment if patients were able to produce sputum. Aerobic cultures were done in the clinical microbiology laboratories of the DVAMC and LDSH. Susceptibilities of the isolates to the study antimicrobial agents were determined by using the Kirby-Bauer method (2) with a 30-μg cephalosporin-class disk.

Treatment and follow-up. Patients were assigned to one of the two treatment regimens by an allocation schedule of random numbers. The two regimens were cephalaxin, 250 mg (Eli Lilly & Co., Indianapolis, Ind.) given orally every 6 h for 10 days, and cefadroxil, 500 mg (Bristol Laboratories, Syracuse, N.Y.) given orally every 12 h for 10 days. Hospitalized patients were observed daily, and outpatients were examined on days 1, 3, 5, and 10 after the start of therapy (DVAMC) or by telephone follow-up every 3 days and a clinic visit at the end of therapy (LDSH). All patients but three (two cefadroxil and one cephalaxin) were initially admitted to the hospital. Adherence to the dosage schedules was evaluated by review of hospital records for inpatients, and for outpatients by telephone follow-up and by determining the number of doses remaining at clinic visits.

Evaluation of efficacy. A case was considered evaluable for efficacy if (i) no other antimicrobial agent was given concomitantly or subsequently and (ii) the response to therapy could be clearly determined. If a patient was validly enrolled in the study on the basis of clinical presentation and initial sputum Gram stain, there was no microbiological requirement that a specific pathogen be isolated from sputum.

The criterion for clinical cure was complete resolution of symptoms and signs of infection. The criteria for clinical failure were (i) the death of the patient during treatment, with infection a contributing factor; (ii) the lack of an objective response to therapy (a continued fever or cough and increase in leukocyte count) after a clinically reasonable period of time; or (iii) a relapse of infection after discontinuation of therapy. Bacteriological cure was defined as eradication of the presumed pathogen at the time the drug was discontinued or at follow-up.

Evaluation of toxicity. Subjects were examined serially for evidence of adverse reactions to the study medications. The following blood tests were performed immediately before and after the cephalosporin therapy and at other times if considered appropriate: hematocrit, leukocyte count with differential, platelet count, blood urea nitrogen, serum creatinine concentration, electrolytes, glutamic oxaloacetic transaminase, bilirubin, and alkaline phosphatase. In addition, chest roentgenograms and urinalyses were done at the beginning and end of treatment and at clinically appropriate intervals.

RESULTS

Thirty-eight patients were considered eligible for the study, and 36 gave informed consent. The other two patients refused to participate. Of those enrolled, two cases were considered un-evaluable because the response to therapy could not be clearly determined.

A total of 34 patients had evaluable infections. Of these, 19 were treated with cefadroxil, and 15 were treated with cephalaxin. The ages of the patients treated with cefadroxil ranged from 19 to 81 years, and of those treated with cephalaxin, from 23 to 92 years. Whites constituted 79 and 80%, respectively, of the patients in the two treatment groups. There were 26 males and 8 females, but 7 of the 8 females were randomized to the cefadroxil group. The presence of medical problems that might predispose to pneumonia in the two groups was comparable (Table 1). The patients enrolled had a variety of other medical diagnoses, including atherosclerotic cardiovascular disease (9), other malignancies (2), hypertension (4), anemia (3), and chronic degenerative (5) and inflammatory (4) disorders; the prevalence of these associated diagnoses in the cefadroxil group (0.84 per patient) and the cephalaxin group (0.74 per patient) was similar. On entry into the study, the duration of patient symptoms, including fever, cough, or change in sputum production, was similar for the cefadroxil and cephalaxin groups (median, 3.5 and 4.0 days, respectively). The initial laboratory parameters of liver and kidney function and hematocrit were normal in most patients, and the mean values were comparable for the cefadroxil and cephalaxin groups. On entry into the study, the leukocyte counts (mean ± standard error) in the peripheral blood of cefadroxil (16,900 ± 1,800) and cephalaxin (13,200 ± 1,400) patients also were similar. S. pneumoniae was isolated in large numbers alone or with another pathogen in 65% of the initial sputum samples (Table 2) and was the most common pathogen;

### Table 1. Predisposing conditions of 34 patients with pneumonia

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cefadroxil group (n = 19)</th>
<th>Cephalaxin group (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Smoking</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Neurological deficit</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Corticosteroid use</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Asthma</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Lung or mediastinal cancer</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Other conditions</td>
<td>2*</td>
<td>1*</td>
</tr>
</tbody>
</table>

* Restrictive lung disease, old shrapnel injuries to lungs.

* Pneumococcosis.
CEFADROXIL TREATMENT OF COMMUNITY PNEUMONIAS

TABLE 2. Bacteriological response in 34 patients with pneumonia

<table>
<thead>
<tr>
<th>Drug and organism</th>
<th>Pretreatment sputum cultures</th>
<th>Posttreatment sputum results</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No further sputum production</td>
<td>Satisfactory sputum specimens produced</td>
<td>Presumed pathogen eliminated</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal flora</td>
<td>4</td>
<td>NA*</td>
<td>NA</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>12</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>S. pneumoniae and H. influenzae</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Beta-hemolytic Streptococcus</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cephalxin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal flora</td>
<td>3</td>
<td>NA*</td>
<td>NA</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>8</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>S. pneumoniae and H. influenzae</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>S. aureus</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*NA, Not applicable.

H. influenzae was isolated from four patients. Normal upper respiratory flora was isolated initially from the sputum of seven patients, but in all of these, sputum Gram stain showed gram-positive diplococci. One of the blood cultures yielded S. pneumoniae. Chest roentgenograms showed single-lobe involvement in 15 of the patients who received cefadroxil and 11 of those who received cephalexin; two or more lobes had infiltrates in 4 patients from each group. Compliance rates were excellent during treatment, with only 17 cefadroxil doses and 12 cephalexin doses not taken.

Of the 34 patients studied, 31 were admitted to the hospital. Ten patients were kept in the hospital for 10 or more days because of other medical problems and thus received all their antibiotic therapy as inpatients. Of the 21 patients who completed antibiotic therapy after discharge, the mean durations in the hospital for the 14 cefadroxil patients (5.1 days) and the 7 cephalexin patients (5.9 days) were not significantly different.

All 34 cases were considered to be clinical cures. No major adverse side effects were noted in either treatment group. Four patients (two cefadroxil and two cephalexin) had mild adverse effects probably not related to their treatment. One patient who received cephalexin had nausea for 4 days but continued his medication to the completion of his course. There were no clinically significant changes in renal or hepatic function or hematocrit during the treatment or follow-up period. One patient treated with cephalaxin developed a transient parapneumonic pleural effusion. Of the 34 patients, 28 were febrile on entry into the study. We were not able to calculate the time until afebrility in seven patients: two because they were treated exclusively as outpatients, two because they were discharged from the hospital still febrile, and three because complete hospital records could not be retrieved. Of the remaining 21 patients, the times until afebrility in the 12 cefadroxil patients (median, 2.5 days) and the 9 cephalexin patients (median, 3.0 days) were not significantly different.

All 22 S. pneumoniae isolates tested were susceptible to cephalosporins (zone size, 26 to 43 mm). At the time of follow-up, clearing or improvement in chest roentgenogram findings was noted in 15 (79%) patients treated with cefadroxil and 11 (73%) patients treated with cephalexin. Fourteen patients were not producing any sputum by the end of treatment. Of the 27 patients from whom a presumed pathogen was isolated initially, 15 were still producing sputum at the time of follow-up, and that organism was eliminated from only 5 (Table 2). The other 10 patients continued to carry the presumed pathogen even though they were clinically improved. No relapses were noted.

DISCUSSION

Although we did not always isolate S. pneumoniae from sputum and only once from blood, its presumed frequent appearance on sputum Gram stains, its frequent isolation from sputum, and the uniformly good clinical response to treatment suggest that as in similar reports (19), S. pneumoniae was the predominant pathogen in the population studied. That only one patient was bacteremic compared with the 30% noted in Austrian's study of pneumococcal pneumonia (1) is further evidence that, as a group, the
patients studied had mild to moderate illnesses. The patients enrolled in this study were frequently debilitated by chronic illnesses and thus might not be considered representative of a population with community-acquired pneumonia. However, past studies of community-acquired pneumonias have shown that preexisting chronic illnesses are common. Since individuals who develop pneumonia do not represent a cross section of the community, the distribution of chronic illness in this population approximates that reported previously (13, 21).

Although the patients enrolled in this study were not so severely ill as to require parenteral therapy, most were initially hospitalized. Because of undefined benefits of hospitalization, it is conceivable that some of these patients on the same regimen taken at home might not have improved as rapidly. However, 24 patients had all or some of their therapy as outpatients, and responses were good. Nevertheless, the very high compliance rates observed might not be achievable under "non-study" conditions.

We found that cefadroxil and cephalaxin were both adequate for treatment of mild community-acquired pneumonia. In all likelihood, penicillin V would have been equally effective, given selection criteria that favored the enrollment of patients with pneumococcal pneumonia. Our single patient with bacteremic pneumococcal pneumonia and three patients from other centers (J. J. Stout, personal communication) all responded to treatment with one of these two agents. All patients recovered from their infections, and the duration of illness until diminution of toxicity, defervescence, and clearing of other symptoms was comparable to that seen in previous studies of antibiotic treatment of community-acquired pneumonia (13, 21). The sole complication was a parapneumonic effusion, and the frequency of this complication (3%) is less than that usually observed with pneumococcal pneumonia (17).

The four patients from whom H. influenzae was isolated are problematic. Although H. influenzae is relatively resistant in vitro to both oral cephalosporins (12), these patients did well. It is possible that these organisms may not have been the etiological agents or that they were sensitive strains. Because resistance to cefadroxil and cephalaxin by H. influenzae is common (12), we do not recommend that either antibiotic be used in the treatment of patients whose initial sputum Gram stains show organisms that appear to be Haemophilus-like. Although Legionella pneumophila has now been shown to be a common cause of community-acquired pneumonia (23), the excellent clinical responses in the patients we studied suggests that it was not a major pathogen. In fact, cephalosporins are not recommended for treatment of infections due to L. pneumophila or Mycoplasma pneumoniae.

The usefulness of cephalaxin treatment for community-acquired pneumonia has been demonstrated (18), but previous studies of cefadroxil have been limited (10). Because of slower renal excretion, cefadroxil persists in the circulation for 1.5 times as long as cephalaxin (90 versus 60 min) (11). The prolonged half-life permits oral administration every 12 h, compared to every 6 h for cephalaxin, a considerable advantage for outpatient treatment in which compliance may be less than ideal. Because the size of the two study groups was limited, small differences in therapeutic effects between these two antibiotics could not have been detected if they had been present.

Our study shows that community-acquired pneumonias that were predominantly due to pneumococci were effectively treated with oral, twice-daily doses of cefadroxil. These data are consistent with results from earlier uncontrolled trials in Argentina and Mexico (3, 14). On the basis of the excellent clinical response seen in this group, we would define as eligible for outpatient oral therapy those patients without clinical evidence for hypoxemia, hypotension, significant signs of toxicity, or severe underlying immunosuppression that would a priori necessitate admission to a hospital, who are judged likely to take oral medication, and who will be available for careful follow-up at frequent intervals.

Although antibiotics have reduced the morbidity and mortality of bacterial pneumonia, the cost of treatment remains surprisingly high. Outpatient treatment of patients with pneumococcal pneumonia cost an estimated $102 (in 1978 dollars) (22), whereas 10 days of hospitalization for pneumonia in 1976 cost $2,000 (10). As financial pressures to manage more patients outside the hospital mount, it is reassuring to note that oral therapy with either cefadroxil or cephalaxin seems as effective as that previously experienced with penicillin V (8). The clinical success of this study suggests that outpatient therapy with cefadroxil or cephalaxin may be appropriate for treating patients with mild or moderate pneumonia.

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