Double-Blind Comparison of Cefamandole and Penicillin in Pneumococcal Pneumonia

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We conducted a prospective, randomized, double-blind comparison of intravenous penicillin and cefamandole in the therapy of pneumococcal pneumonia. Patients received either 1 g of cefamandole or 600,000 U of aqueous penicillin G every 6 h. Of the 100 patients entered into the study, 96 had clinical and radiographic evidence of pneumonia. Microbial etiology was determined from the results of sputum and blood cultures and/or sputum Gram stains. Streptococcus pneumoniae was pathogenic in 49 patients, of whom 24 received cefamandole and 25 received penicillin. There was no statistically significant difference in the response or cure rate. Of the 100 patients, 93 were treated for 3 days or more and were evaluated for adverse effects and toxicity. There was no significant difference between cefamandole-treated and penicillin-treated patients in the incidence of colonization, superinfection, phlebitis, thrombocytopenia, decrease in hematocrit, or elevated liver function tests. Eosinophilia occurred more frequently in patients treated with penicillin (20 of 42) than in those treated with cefamandole (11 of 42) (chi square, P < 0.05). Only one patient receiving cefamandole developed a positive direct Coombs test. No patient in either group developed meningitis. We conclude that, with the doses and route of administration employed in this study, cefamandole is as effective as penicillin in the therapy of pneumococcal pneumonia without an increased incidence of colonization, superinfection, or adverse effects.

Patients with pneumonia can be a diagnostic problem for physicians. Present methods for determining the pathogen in this setting may be inaccurate, making selection of an appropriate antibiotic difficult. For example, the sputum examination and culture may be imprecise, particularly if improper techniques are used, and reliance on these methods can lead to an incorrect initial diagnosis (2, 10, 11). Even pneumococcal pneumonia, the most common bacterial pneumonia, may be misdiagnosed. Pneumonia due to other serious penicillin-resistant pathogens such as Staphylococcus aureus and Haemophilus influenzae may be initially mistaken for pneumococcal pneumonia and inappropriately treated.

Because of the difficulty in reaching an accurate diagnosis before culture results are available, it might be appropriate to initially treat a patient presumed to have pneumococcal pneumonia with an agent effective not only against pneumococci, but also against the other common pathogens, particularly if the patient is seriously ill. Cefamandole, a new cephalosporin antibiotic, provides such broad-spectrum coverage, with activity against Streptococcus pneumoniae, S. aureus, and many gram-negative organisms including H. influenzae and Klebsiella pneumoniae (7, 9). However, cefamandole would not be an acceptable alternative to penicillin if it caused more adverse effects, colonization, or superinfection, or was less effective in eradicating the pneumococci. To investigate these issues, we conducted a randomized, prospective, double-blind comparison of cefamandole and penicillin in the treatment of patients with presumed or proven pneumococcal pneumonia.

MATERIALS AND METHODS

One hundred adult patients with community-acquired pneumonia, who had been hospitalized on the medical service of the Johns Hopkins Hospital, Baltimore, were admitted to the study. A patient was entered into the study if a diagnosis of pneumococcal pneumonia was made by the house officer or attending physician and if, under normal circumstances, penicillin would have been administered. The initial evaluation of the illness of each patient was performed by his or her primary physician and included a history, a physical examination, and a leukocyte (WBC) count,
as well as differential, chest radiograph, and sputum examinations. In addition, if a patient was admitted to the study, blood and sputum cultures, hematocrit, platelet count, direct Coombs test, serum creatinine, serum glutamic oxaloacetic transaminase (SGOT), serum alkaline phosphatase, and total bilirubin were obtained. All of these measurements were repeated regularly throughout the treatment period and at 7 to 30 days after therapy was discontinued, if the patient returned for a follow-up visit. Each patient gave informed consent before entry into the study.

Criteria for exclusion from the protocol were (i) antibiotic therapy within 3 days, (ii) pregnancy, (iii) allergy to penicillin or cephalosporins, (iv) meningitis, and (v) a need for concurrent use of a second systemic antibiotic. Treatment was randomized such that patients received either 1 g of cefamandole or 600,000 U of aqueous penicillin G intravenously every 6 h. Therapy was discontinued if: (i) the patient was afebrile for at least 4 consecutive days; (ii) a potentially resistant pathogen was recovered from the blood or in moderate to heavy growth from the sputum; (iii) any adverse reaction occurred; or (iv) the patient deteriorated and failed to respond to treatment within 72 h after the antibiotic was started.

Response was defined as (i) a decrease in temperature by 1°F (0.6°C) or to normal, (ii) a decrease in the WBC count by at least 15% or to normal, and (iii) diminution in the severity of symptoms. Cure was defined as (i) response, (ii) clearing of the sputum and/or blood of pathogens, (iii) no recurrence of fever or other symptoms, and (iv) improved or normal chest radiograph at the follow-up visit. Evaluation for cure depended on successful completion of the course of antibiotic therapy, the patient returning for post-therapy evaluation and receiving no antibiotic therapy after the study drug was discontinued.

Supernfection was defined as the development of clinical evidence of a new infection in the lungs or at a distant site and identified by isolation from cultures of the site of a pathogen that was not originally present. Colonization was defined as the presence, in a sputum culture, of a potential pathogen that was not present in the initial culture but without evidence of superinfection.

An absolute eosinophil count of greater than 250/mm³, a platelet count of greater than 400,000/mm³, and a decrease in hematocrit of 5% or greater were defined as abnormal. An increase in serum creatinine or liver function tests above the 95% confidence limit in our laboratory from the pretherapy value was considered abnormal. For serum creatinine, this meant an increase of more than 0.4 mg/dl, and for total bilirubin it meant an increase of at least 1.0 mg/dl to be considered abnormal. Only patients treated for 3 days or longer were evaluated for toxicity.

Either transtracheal or expectorated sputum specimens were collected and transported to the microbiology laboratory with 2 h. Samples of the sputum were immediately streaked onto chocolate, 5% sheep blood, or MacConkey agar and incubated in CO₂ at 37°C. Cultures were examined at 24 and 48 h. S. pneumoniae were identified by colony morphology and optochin sensitivity.

The pathogen causing illness in each patient was determined by the results of blood and sputum cultures, as well as review of the sputum Gram stain in a blind fashion by the investigators and by an independent clinical microbiologist. The sputum stain was considered diagnostic of pneumococcal pneumonia if: (i) there were less than 10 squamous cells per low-power field; (ii) polymorphonuclear leukocytes or alveolar macrophages were present; and (iii) the predominant organisms present were gram-positive diplococci, without remarkable numbers of other organisms.

The diagnosis of pneumococcal pneumonia was based on the presence of an infiltrate on chest X-ray in the setting of an acute respiratory illness and the presence of either (i) a moderate to heavy growth of S. pneumoniae from sputum cultures, (ii) a sputum smear that fulfilled our criteria for a diagnostic Gram stain or (iii) growth of S. pneumoniae from blood or transtracheal aspirate cultures.

RESULTS

Of the 100 patients entered into the study, 96 had radiographic evidence of pneumonia. Of these, 49 (51%) had pneumonia attributed to S. pneumoniae alone, by our criteria. Three patients had pneumonia attributed to S. pneumoniae plus another pathogen, and 13 patients had pneumonia attributed to various nonpneumococcal, gram-positive and/or gram-negative organisms. In 31 patients, no definite pathogen was demonstrated.

Of the 49 patients with pneumonia due solely to S. pneumoniae, 24 were treated with cefamandole and 25 were treated with penicillin. Demographic data for these patients are included in Table 1. There was no significant difference due to the age, sex, initial WBC count, initial temperature, or underlying diseases of the patients, or to the duration of therapy.

Of the 10.2% with pneumococcal pneumonia had positive blood cultures and 36 (73.5%) had positive sputum cultures (Fig. 1). Fifteen of these cultures were obtained by transtracheal aspiration. Sputum stains were available in 47 cases, and 37 (78.7%) had a diagnostic sputum stain. Of the 36 patients with positive sputum cultures, Gram stains were available for 34, and 25 (73.5%) were diagnostic.

Of the 37 patients with sputum stains thought to be diagnostic of pneumococcal pneumonia, 25 (67.8%) had positive sputum cultures for pneumococcus. 2 were positive for nonpneumococcal streptococci, 1 was positive for K. pneumoniae, and 9 grew only normal respiratory flora. The minimal inhibitory concentration of cefamandole for pneumococci was ≤0.5 μg/ml, except for one organism for which it was 1 μg/ml. Penicillin susceptibility was tested in 21 pneumococci.
Minimal inhibitory concentrations for 7, 11, and 3 of the pneumococci were <0.1, 0.1, and >0.1 μg of penicillin per ml, respectively.

Of the 49 patients with pneumonia due to S. pneumoniae, all 24 treated with cefamandole and all 25 treated with penicillin responded to therapy (Fig. 2). Follow-up appointments were made for all patients who completed the protocol, but only 17 of the group treated with cefamandole (70.8%) and 14 treated with penicillin (56%) returned. Of those who were seen at follow-up, only one patient in each group was not cured. In the cefamandole group, one patient was judged a failure because his chest radiograph did not improve after treatment, although he became asymptomatic and afebrile. Within 1 month, the cause was found to be lung carcinoma. The failure on penicillin therapy had an excellent initial response and was afebrile for 5 days. On day 7, however, the fever spiked, and blood cultures were positive for Enterobacter cloacae. Her chest radiograph was much improved compared with that at the time of admission, and no potential source for this infection except her indwelling intravenous catheter could be found. There was no significant difference in the course of those patients with pneumococcal pneumonia treated with either antibiotic. Twenty of 24 patients (83.3%) treated with cefamandole and 20 of 25 patients (80%) treated with penicillin were afebrile by the second full day of therapy (Fig. 2). A decrease in WBC count of at least 15% or to normal was achieved in 21 of 23 patients (91.3%) in both groups by day 3.

After the clinical data were reviewed, 13 patients were believed to have bacterial pneumonia due to nonpneumococcal pathogens (Table 2). In each case, the initial sputum Gram stain was interpreted by the physician of the patient as indicating infection with S. pneumoniae. Three types of errors were made by the physicians in interpreting these stains: (i) interpretation of poor-quality stains, (ii) misidentification of the species of gram-positive cocci, and (iii) failure to recognize the presence of gram-negative organisms on the slides. These patients were switched to other antibiotics after it became known that their infection was not pneumococcal. Because of the small numbers of patients, varied duration of therapy, and variety of pathogens, we can make no statement regarding efficacy of either agent in this group. The 31 patients with no demonstrable pathogen had a response and cure rate in excess of 90% with

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean age (yr)</th>
<th>Sex (male/female)</th>
<th>Mean initial WBC x 1,000</th>
<th>Mean initial temp (°F)</th>
<th>Alcohol abuse</th>
<th>Obstructive lung disease</th>
<th>Lung carcinoma</th>
<th>Mean days of therapy</th>
<th>Bacteremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefamandole (24 patients)</td>
<td>52 (21-89)</td>
<td>19/5</td>
<td>14.6</td>
<td>102.9±34.9</td>
<td>11</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>6.8 (4-13)</td>
</tr>
<tr>
<td>Penicillin (25 patients)</td>
<td>46 (21-92)</td>
<td>15/10</td>
<td>14.1</td>
<td>102.4±25.7</td>
<td>12</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>5.7 (4-9)</td>
</tr>
</tbody>
</table>

* Ranges appear in parenthesis below mean values.
± Approximately 38.4°C.
*± Approximately 39.1°C.
TABLE 2. Clinical data on 13 patients with nonpneumococcal pneumonia

<table>
<thead>
<tr>
<th>Pneumonia</th>
<th>Gram stain review</th>
<th>Sputum culture</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcal</td>
<td>Gram-positive cocci</td>
<td>Group A, beta-hemolytic streptococcus</td>
<td>Pure growth—transtracheal aspirate</td>
</tr>
<tr>
<td>Streptococcal</td>
<td>Gram-positive cocci</td>
<td>Group A, beta-hemolytic streptococcus</td>
<td>Pure growth—transtracheal aspirate</td>
</tr>
<tr>
<td>Staphylococcal</td>
<td>Gram-positive cocci</td>
<td>Staphylococcus aureus</td>
<td>Predominant, heavy growth</td>
</tr>
<tr>
<td>Staphylococcal</td>
<td>Gram-positive cocci</td>
<td>S. aureus</td>
<td>Predominant, heavy growth</td>
</tr>
<tr>
<td>Staphylococcal</td>
<td>Gram-positive cocci</td>
<td>S. aureus</td>
<td>Predominant, heavy growth</td>
</tr>
<tr>
<td>Staphylococcal</td>
<td>Poor quality</td>
<td>S. aureus</td>
<td>Pure growth—transtracheal aspirate</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>Gram-positive cocci</td>
<td>Klebsiella pneumoniae</td>
<td>Predominant, heavy growth</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>Gram-negative bacilli</td>
<td>Klebsiella pneumoniae</td>
<td>Predominant, heavy growth</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>Poor quality</td>
<td>K. pneumoniae</td>
<td>Predominant, heavy growth</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>Poor quality</td>
<td>Pseudomonas maltophilia</td>
<td>Blood culture positive</td>
</tr>
<tr>
<td>Mixed</td>
<td>Gram-positive cocci</td>
<td>S. aureus</td>
<td>Heavy growth, both pathogens</td>
</tr>
<tr>
<td>Mixed</td>
<td>Gram-negative bacilli</td>
<td>K. pneumoniae</td>
<td>Transtracheal aspirate</td>
</tr>
<tr>
<td>Mixed</td>
<td>Gram-positive cocci</td>
<td>K. pneumoniae</td>
<td>Transtracheal aspirate</td>
</tr>
<tr>
<td>Mixed</td>
<td>Gram-negative bacilli</td>
<td>Enterobacter aerogenes and E. cloacae</td>
<td>Transtracheal aspirate</td>
</tr>
<tr>
<td>Mixed</td>
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<td>S. aureus</td>
<td>Transtracheal aspirate</td>
</tr>
<tr>
<td>Mixed</td>
<td>Gram-positive cocci</td>
<td>Streptococcus pneumoniae</td>
<td>Transtracheal aspirate</td>
</tr>
<tr>
<td>Mycoplasma</td>
<td>Normal flora</td>
<td>Normal flora</td>
<td>Titer rise from 1:8 to &gt;1:500</td>
</tr>
</tbody>
</table>

* All stains were interpreted by the housestaff physicians as indicating infection with S. pneumoniae.

either antibiotic, and there was no significant difference between the two treatment groups.

Six patients died during or shortly after the course of the protocol. The causes of death were pulmonary embolus (one), myocardial infarction (two), lymphoma (two), and disseminated bronchogenic carcinoma (one). The determination of the cause of death was based on the clinical course of each patient. Since the study was double-blind, this evaluation was unbiased. No patient with pneumococcal pneumonia, not even those with bacteremia, died as a result of the infection.

Of the 93 patients treated for 3 days or more and evaluated for toxicity, 47 were treated with cefamandole and 46 were treated with penicillin. No significant difference existed between those who received cefamandole and those who received penicillin, with regard to mean age (52 versus 45 years, respectively), duration of therapy (6.6 versus 6.4, respectively), or underlying diseases (alcoholism and chronic obstructive lung disease). More of the patients receiving cefamandole were male (79% cefamandole versus 60% penicillin).

One adverse effect of cefamandole therapy was that one patient developed a positive direct Coombs test. A mild hemolytic process may have been associated with this abnormality, but absolute evidence is lacking. Thrombocytosis, elevated liver function tests, and a fall in hematocrit levels occurred after both kinds of therapy (Table 3). About 5% of the patients in both groups developed an unexplained increase in serum creatinine; the differences between penicillin- and cefamandole-treated patients were not statistically significant. Eosinophilia occurred more often in patients treated with penicillin than in those treated with cefamandole, although no other evidence of hypersensitivity developed in any of these patients.

Colonization occurred in 13 of 47 patients (27.7%) treated with cefamandole and 9 of 46 patients (19.6%) treated with penicillin. Super-
infection was uncommon. Only one patient treated with cefamandole became superinfected (2.2%); this was 2 days after ampicillin was substituted for cefamandole and after two unsuccessful attempts at gastroscopy. The patient developed a Pseudomonas pneumonia, diagnosed bacteriologically on the basis of sputum and blood cultures that grew P. maltophilia. Four patients treated with penicillin (8.7%) became superinfected, three with gram-negative urinary tract infections and one with E. cloacae sepsis. None of these patients had an indwelling Foley catheter. The difference in superinfection and colonization rates was not statistically significant. Interestingly, none of the patients in either group developed a pulmonary superinfection while being treated with penicillin or cefamandole. No patient in either group developed meningitis, including four patients with pneumococcal bacteremia who were treated with cefamandole.

**DISCUSSION**

In our study, the diagnosis of pneumococcal pneumonia was based on the results of sputum Gram stains, sputum cultures, and blood cultures. In 18 patients, blood cultures and/or transtracheal aspirate cultures grew S. pneumoniae. The remainder of the patients had a predominant growth of S. pneumoniae on sputum culture, and/or the sputum Gram stain was interpreted as indicating infection with pneumococci. The diagnostic value of these techniques has been evaluated. Thorsteinsson et al. (13) have recently demonstrated that sputum cultures are reliable in diagnosing pneumococcal pneumonia, although they were previously reported to be of little value (2). Murray and Washington have correlated the results of sputum Gram stains with transtracheal aspirate cultures and shown a good correlation, provided the slide being evaluated contains less than 10 epithelial cells per low-power field (8). In our series, interpretation of poor slides led to the improper diagnosis of streptococcal, mycoplasma, staphylococcal, and klebsiella pneumonia, emphasizing the importance of using strict criteria when interpreting Gram stains. We reviewed our slides by using established criteria and had our slides reviewed blindly by an independent microbiologist. In addition, our cases were evaluated in a double-blind manner, thus eliminating the possibility of bias.

Both cephaloridine and lincomycin have been compared with penicillin G in the treatment of pneumococcal pneumonia. Tempest and Austrian compared 1 g of cephaloridine per day given intramuscularly (i.m.) with 600,000 U of penicillin per day given i.m. and found no difference in efficacy (12). Anderson et al. compared 1.2 g of lincomycin per day given i.m. with 600,000 U of penicillin G per day given i.m. and found similar results (1). Cherubin et al. compared 1.2 g of lincomycin per day i.m., 2 g of cephaloridine per day i.m., and 1.2 × 10⁶ U of procaine penicillin per day i.m. and found that these regimens were equally effective (4). Our study differs from these reports in three ways: (i) we evaluated an antibiotic, cefamandole, that is effective against all of the organisms that commonly cause bacterial pneumonia, including H. influenzae; (ii) we evaluated the incidence of colonization and superinfection; and (iii) our study was double-blind, thus eliminating the possibility of bias. We have found that there is no statistically significant difference between 4 g of cefamandole per day and 2.4 × 10⁶ U of penicillin G per day, and, due to the size of our study, we could exclude differences of 25% or greater.

In contrast to the other comparative trials, we evaluated the incidence of colonization and superinfection. Louria and Brayton (5) and Tillotson and Finland (14) have reported that doses of penicillin G greater than 2.4 × 10⁶ and 3.0 × 10⁶ U/day result in a higher incidence of colonization and superinfection. Tillotson and Finland (14) have suggested that broad-spectrum antibiotics are also associated with an increased incidence of these adverse effects. We found a low incidence of colonization and superinfection by using a dose of 2.4 × 10⁶ U of penicillin per.
day. However, we did not find an increase in colonization and superinfection by using 4 g of cefamandole per day. As with penicillin, this phenomenon may be dose related. However, Benner could not find an increased incidence of superinfection in patients treated for pneumococcal pneumonia with either 6 to 8 g of cephalothin, 4.5 to 10 g of lincomycin, or 4 g of cephaloridine per day when he evaluated these patients with transtracheal aspiration (3). Our dose of cefamandole was low, and it may be that larger doses would result in an increase, although the data of Benner argue against this.

We have demonstrated that: (i) improper technique can lead to errors in interpreting sputum Gram stains, resulting in improper treatment of patients with pneumonia; (ii) cefamandole was as effective as penicillin in the treatment of pneumococcal pneumonia; and (iii) when compared with penicillin, treatment with 4 g of cefamandole did not result in an increased risk of colonization or superinfection.

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LITERATURE CITED


