Ampicillin and Tetracycline in the Treatment and Prophylaxis of Chronic Bronchitis


Departments of Medicine, University of Washington and Harborview Medical Center, Seattle, Washington 98104

Received for publication 24 April 1972

Ampicillin and tetracycline, in doses of 2 g a day, were compared in the treatment of acute exacerbations of chronic bronchitis. Seventy-nine patients were followed for 3 to 29 months and were treated for 118 exacerbations. Clinical improvement occurred after 10 days of treatment with either drug in over 80% of the cases. Haemophilus influenzae and Diplococcus pneumoniae were eradicated from the sputum more than 60% of the time, but in general there was a poor correlation between bacteriologic clearing and clinical response. The effect of chemoprophylaxis with ampicillin and tetracycline in doses of 1 g a day on the frequency of acute exacerbations of bronchitis was compared with that of a placebo. Seven hundred eighty prophylactic regimens, consisting of one capsule every 12 hr for 5 days beginning with the first sign of a cold, were prescribed for 76 patients. Irrespective of the regimen, an acute exacerbation of bronchitis was encountered at approximately 13% of the follow-up visits to the clinic.

Bacterial infection is probably not a primary etiologic factor in the development of simple chronic bronchitis in most patients. However, infection of the lower respiratory tract with a variety of bacteria including the potential pathogens Haemophilus influenzae and Diplococcus pneumoniae is almost universal in this disease (4, 8), and it is generally recommended that patients with chronic airways obstruction receive antibiotics when they show signs of acute infection.

Although most studies have indicated that tetracycline and ampicillin in doses of 1 g daily are equally effective in the treatment of acute exacerbations of bronchitis (1, 3, 9), May and Delves reported that ampicillin was slightly superior at these doses and at 4 g daily it clearly gave better results (10). The current study was undertaken to evaluate the relative effectiveness of ampicillin and tetracycline in the treatment of acute exacerbations of chronic bronchitis at an intermediate dose of 2 g daily. The use of these drugs prophylactically at the first sign of a respiratory tract infection was also evaluated.

MATERIALS AND METHODS

Patients. One hundred fifty three patients with chronic bronchitis (according to the definition of the American Thoracic Society [2], i.e., productive cough on most days three months out of the year for at least two successive years), were enrolled in the study during the 2.5 years it was in progress. The clinic records of 79 of these patients were sufficiently complete for analysis and form the basis of this study. These patients were followed for 3 to 29 months; there were 68 men and 11 women, with an average age of 60.5 years. Most of the patients had airways obstruction, and the mean forced expiratory volume in one second (FEVy) of the group on entrance to the study was 1.33 liters, with a range of 0.5 to 2.9 liters.

Protocol. Patients did not receive antibiotics during the first month in the study. In addition to history and physical examination, each patient had a chest X ray, hematocrit, leukocyte count, eosinophile count, urinalysis, routine blood chemistries, electrocardiogram, tuberculin and fungal skin tests, and screening pulmonary function tests as part of their initial evaluation. Patients were instructed to collect all the sputum they produced during the 24 hr prior to each clinic visit. The volume of these samples was measured, and the sputum was characterized arbitrarily as mucoid or purulent on the basis of visual assessment and the amount of foam produced in a standard test tube when 1 ml of hydrogen peroxide was mixed with 1 ml of sputum. At each visit, shortness of breath was graded according to an arbitrary scale, the FEVy was measured, and freshly expectorated sputum was collected for quantitative bacterial cultures.

Patients were assigned to one of four antibiotic regimens for treatment and prophylaxis in a random, double blind manner (Table 1). All patients received either tetracycline or ampicillin for treatment, but half received a placebo for prophylaxis. (Identical unmarked capsules containing a placebo or 500 mg of tetracycline or ampicillin were supplied by Bristol Laboratories.)

Each patient initially received a therapeutic course...
of antibiotics. Subsequently, either therapy or prophylaxis was prescribed at each clinic visit depending on whether a patient was judged to have an acute exacerbation of bronchitis or not. The criteria used for this determination are: (i) purulent sputum (> 50% pus) or (ii) any three of the following: significant increase in cough and sputum production, moist rales not present on previous examination of the chest, fever, leukocytosis, FEV₁, reduced to two-thirds or less of the patient’s usual volume, or dyspnea on exertion at least one grade worse than usual. In most instances, the development of purulent sputum was associated with one or more of the criteria listed in (ii). When a therapeutic course of antibiotic was prescribed, the patient returned to the clinic in 14 days. If signs of the exacerbation persisted, the therapeutic course was repeated. If the exacerbation failed to clear after the second course, the patient was dropped from the study, and a treatment failure was charged to the drug.

When a prophylactic regimen was prescribed, patients were instructed to take the full course of antibiotic at the first sign of a cold. These patients were followed at monthly intervals; if they used their prophylactic medication between visits, it was re-issued unless they had an acute exacerbation which required treatment. Every 5 months, patients were automatically switched to an alternate regimen according to a predetermined pattern. Other aspects of the management of these patients were not controlled in this study.

**Bacteriology.** The freshly expectorated sputum sample collected at each clinic visit was homogenized by mixing equal volumes of sputum and a 0.5% solution of acetylcysteine at room temperature for 5 min. The homogenized sputum was diluted serially in Trypitcase soy broth, and 0.1 ml of each dilution was cultured on blood and chocolate agar media. Plates were incubated 18 to 24 hr at 37 C in an atmosphere containing 5% CO₂. The five most numerous species of bacteria in each sample of sputum were identified by standard microbiological techniques.

## RESULTS

**Effect of antibiotics on acute exacerbations.**

**Clinical.** Ampicillin was used to treat 60 exacerbations of bronchitis, and tetracycline was used in 58. The sputum converted from purulent to mucoid in 82% of the patients receiving a single course of therapy with ampicillin, whereas one course of tetracycline induced a remission in 91% of the exacerbations. This apparent difference is not statistically significant ($\chi^2 = 2.3; P > 0.10$). With both antibiotics, a few additional exacerbations were cleared with a second course of therapy, so the failure rate with ampicillin was 13% as opposed to 4% with tetracycline.

When treatment with either antibiotic was associated with clearing of sputum purulence, patients almost invariably claimed to feel better. However, their sputum volume and grade of dyspnea showed no consistent change with therapy.

(ii) **Bacteriology.** *H. influenzae* and *D. pneumoniae*, or both, were recovered from the sputum of 74% of the patients with acute exacerbations of bronchitis. In 50% of the exacerbations, *H. influenzae* was the only likely pathogen recovered, and in 10% *D. pneumoniae* was recovered alone. The numbers of organisms encountered ranged from $10^4$ to $10^9$ per ml. Nonpathogenic bacteria most frequently recovered included *Neisseria* species and alpha or nonhemolytic streptococci. *H. influenzae* was eradicated from the sputum in 72% of the exacerbations treated with tetracycline, but in only 40% of those treated with ampicillin. This difference is statistically significant ($\chi^2 = 7.202; P < 0.01$). *D. pneumoniae* was eliminated from the sputum 67% of the time with tetracycline and 93% of the time with ampicillin. However, this organism was not recovered with sufficient frequency to validate this difference statistically.

Clearing of sputum purulence did not depend entirely on reduction in number or eradication of potential pathogens. In about 35% of exacerbations, *H. influenzae* and *D. pneumoniae*, or both, were present in the sputum in large numbers 3 days after therapy was discontinued. When organisms were eliminated from the sputum by treatment, they usually reappeared in large numbers within 6 to 12 weeks. However, this bacteriological change was rarely accompanied by an acute exacerbation of bronchitis.

**Pulmonary function.** Monthly measurements of vital capacity and FEV₁ were available on 46 patients followed for more than 1 year. For some patients, there was marked variation in results from month to month, whereas others maintained stable function throughout the period of study. In general, the FEV₁ was not decreased by an acute exacerbation of bronchitis, and conversion of the sputum from purulent to mucoid was only rarely associated with improvement in
the FEV₁. The mean FEV₁ for the entire group declined at the rate of about 80 ml per year.

**Effect of chemoprophylaxis.** There were sufficient data on 76 patients to evaluate the effect of prophylaxis on the incidence of acute exacerbations of bronchitis. A prophylactic regimen was prescribed 780 times (one capsule every 12 hr for 5 days for 76 patients), and the patients were seen again within 4 to 8 weeks; a placebo was dispensed 354 times, and ampicillin or tetracycline were dispensed 213 times each (Table 2). Irrespective of the regimen prescribed, an acute exacerbation was encountered at approximately 13% of the follow-up visits to the clinic. Although patients were instructed to take their drug only if they developed symptoms of a cold, most of them took the prescribed drug at some time between visits. When these results were analyzed only for those visits at which self administration of prophylaxis was carefully documented by history, the numbers were smaller, but the proportion of visits at which an acute exacerbation of bronchitis was encountered was still the same in all groups.

No effort was made to evaluate the effect of chemoprophylaxis on the severity of an acute attack of bronchitis.

**DISCUSSION**

The role of bacterial infection in the etiology of acute exacerbations of chronic bronchitis is not clear. Two separate lines of evidence suggest that most exacerbations are triggered by viral infection or by other factors such as atmospheric pollution rather than bacterial infection. Firstly, it was shown that rhinovirus infection in patients with chronic bronchitis usually causes a full-blown acute exacerbation, whereas in normal individuals it usually causes afebrile rhinorrhea (12). Secondly, studies have been reported in which chemoprophylaxis with a variety of antimicrobial agents failed to influence the frequency with which acute exacerbation of bronchitis occurred, suggesting that bacterial infections rarely initiated exacerbations (6, 11). This is a controversial point, because others have reported a decrease in the number of exacerbations in patients receiving chemoprophylaxis during the winter (7). However, virtually all of these studies have demonstrated that administration of antibiotics significantly reduced the severity of exacerbations.

The results of the current study show that ampicillin and tetracycline are about equally effective in treating acute exacerbations of bronchitis. Sputum routinely converted from purulent to mucoid with therapy, and patients almost invariably were subjectively improved despite the fact that the sputum volume, grade of dyspnea, and FEV₁ usually were unchanged. Over 60% of the time, *H. influenzae* and *D. pneumoniae* were eradicated from the sputum by therapy. However, about one-third of the exacerbations responded despite persistence of these organisms, and clinical exacerbation usually did not accompany reappearance of potential pathogens in the sputum.

The only significant difference between tetracycline and ampicillin noted in this study was the higher frequency with which tetracycline eradicated *Haemophilus* species from the sputum. Amoxicillin more consistently eradicated pneumococci, but the numbers were too small to substantiate this difference statistically. In view of the relatively poor correlation between clinical and bacteriological response to therapy, it is questionable whether either of these observations has practical meaning.

The failure of chemoprophylaxis initiated at the first sign of an upper respiratory tract infection to protect against development of acute exacerbations is not surprising. It was not possible in this study to assess the severity of exacerbations which developed in patients treated with placebo versus antibiotic, but others have shown that antibiotics administered early in the course of an exacerbation significantly modify its course. Therefore, if prophylaxis is recommended, it should be with this goal in mind, and intermittent administration of drugs should be as effective and less expensive than continuous prophylaxis.

All studies of this type suffer from the fact that too little is known about the role of bacterial infection in the etiology, pathogenesis, and natural history of chronic bronchitis. A study of patients with bronchitis in association with bronchiectasis indicated that those with frequent exacerbations had a higher mortality and more rapid deterioration of lung function over a period of years (5). However, similar data are not available for patients with chronic bronchitis and obstructive pulmonary disease, and the use of antibiotics in this group is largely empiric. This and other studies indicate that ampicillin and

---

**Table 2. Effect of antimicrobial prophylaxis on the incidence of acute exacerbations of bronchitis**

| Antibiotics | No. of prophylactic regimens | Subsequent exacerbations
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>213</td>
<td>27</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>213</td>
<td>29</td>
</tr>
<tr>
<td>Placebo</td>
<td>354</td>
<td>48</td>
</tr>
</tbody>
</table>
tetracycline are about equally effective in treating acute exacerbations of bronchitis, so the choice should depend on cost, history of allergy, and other factors.

ACKNOWLEDGMENTS

The authors are grateful for the technical assistance of Lorene Seeley, Judy Condon, and Joyce Mazza.

This investigation was supported by Bristol Laboratories and Public Health Service grants AI 00146, AI 43,518, and AI 43,727 from the National Institute of Allergy and Infectious Diseases, and grants HE 5819 and HE 10289 from the National Heart Lung Institute. The studies were conducted at the University of Washington Clinical Research Center at Harborview Medical Center and were supported by grant RR-133 from the General Clinical Research Center Program of the Division of Research Resources, National Institutes of Health.

LITERATURE CITED