A Controlled Trial of Ambroxol in Chronic Bronchitis*

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Ambroxol is a mucolytic agent which is widely used in chronic bronchitis in Europe. We conducted a double-blind randomized controlled trial of ambroxol vs matched placebo in 90 patients with chronic bronchitis and difficulty clearing secretions. It was concluded that there was no advantage to taking ambroxol.

Ambroxol (Mucosolvan) is widely used as a mucolytic agent in Europe. Experimental data suggest biologic reasons why the drug might be effective, and a single randomized controlled trial (RCT) has suggested that the drug may be of benefit in helping patients to clear secretions. However, the previous RCT used multiple outcome measures, only one of which was positive; no correction for the use of multiple outcomes was made. We therefore conducted a randomized trial of ambroxol in patients with chronic bronchitis who had difficulty raising secretions.

METHODS

Sample Specification

The target population for the study was patients with chronic cough and difficulty raising sputum. We identified two groups, or strata, of such patients. Inclusion criteria for both strata included the following:

1. Daily cough productive of sputum for at least the previous three months.
2. Difficulty expectorating sputum.
3. Compliance in the use of a diary card and peak flow meter during the initial run-in period.
4. A smoking history of at least ten pack-years.

In addition, patients in the first stratum met the following criteria:

1. Forced expiratory volume in 1 second (FEV₁) greater than 70 percent of predicted. Ratio of FEV₁ to vital capacity (VC) greater than 0.7.
2. Currently smoking at least two packs of cigarettes per week.

Patients were excluded from the first stratum if they were currently taking, or had previously taken on a regular basis, oral or inhaled bronchodilators.

Patients in the second stratum had impaired respiratory function, defined as follows:

1. FEV₁ less than 70 percent of predicted and FEV₁ to VC ratio less than 0.7.

Exclusion criteria for both groups included the following:

1. Patients identified by their clinicians as having asthma or atopy.
3. Previous or present bronchial carcinoma or tuberculosis.
4. Ongoing acute upper respiratory tract infection.

Stratum 1 patients were recruited primarily through media advertising. Stratum 2 patients were recruited primarily through a respiratory registry of all patients with FEV₁ less than 70 percent of predicted and FEV₁ to VC ratio less than 0.7 seen at three respirology group practices over the preceding three years.

Study Design

Patients who accurately completed a symptom diary during a one week run-in period were randomized to receive ambroxol, 60 mg bid, or matched placebo during the subsequent four weeks. Investigators, patients, and research staff were blind to allocation. Measures of outcome were obtained at baseline, two and four weeks as follows:

1. Peak flow measurements were obtained using a peak flow meter each day in the early morning and evening.
2. The FEV₁ and forced vital capacity (FVC) and midexpiratory flow rates (FEF 25-75) were obtained from the best of three expirations into a Collins water spirometer with a 420 microproces-
3. Using established principles, a questionnaire measuring key symptoms was constructed. Questions focused on symptoms which ambroxol was thought to ameliorate: cough, sputum production, and difficulty expectorating sputum. Response options for each question were framed as a seven point Likert scale (for example, patients were asked to characterize their difficulty expectorating sputum as extremely difficult; very difficult; quite difficult . . . not at all difficult). Following the study, the subjects were asked to make a global rating of whether the medication had helped their cough, sputum, and difficulty expectorating.
4. A diary, a simplified version of the symptom questionnaire, was completed daily by each patient.

The four-week treatment period was chosen on the basis of the prompt response to ambroxol seen in animal models and the prompt response reported in uncontrolled trials in human beings.

Statistical Methods

At the start of the study, we did not know the variability associated with questionnaire scores, nor the minimal clinically important difference. Therefore, to determine sample size, we specified that if the treated group were as much as one standard deviation better off than the control group, we wished to be able to detect this difference. Setting alpha equal to 0.05 and beta equal to 0.10 would require 20 subjects per group. Since we wished to detect this difference if it existed in either patients with our without airflow obstruction, 20 patients per group were required for both sets of patients.

The first three primary outcome variables were analyzed using a
Table 1—Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ambroxol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male 24/45</td>
<td>Male 23/45</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56.6 ± 2.1†</td>
<td>56.0 ± 1.7</td>
</tr>
<tr>
<td>No. of cigarettes/day</td>
<td>20-40</td>
<td>27</td>
</tr>
<tr>
<td>Duration of smoking (yr)</td>
<td>34.7 ± 2.2</td>
<td>35.6 ± 1.9</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>2.14 ± 0.15</td>
<td>2.00 ± 0.12</td>
</tr>
</tbody>
</table>

*Mean ± SEM.

repeated measures analysis of variance of the difference scores between baseline and two and four week follow-up visits. The diary card was analyzed using a repeated measures analysis of variance. The proportion of patients reporting overall improvement was compared using a chi-square test. Confidence intervals (95 percent) around the differences between the two groups were calculated. For the proportion of patients responding, the number of subjects required to exclude a 25 percent risk reduction for ambroxol was calculated.⁴

RESULTS

Because results were virtually identical in the two strata, they will be presented together. For some of the baseline characteristics and outcomes, data were missing from one or two subjects. The baseline characteristics of the 90 subjects who began the run-in period are presented in Table 1. The groups are comparable, and none of the small differences observed reached conventional levels of statistical significance. Of the 45 subjects randomized to ambroxol, eight dropped out prior to completing the study. Four patients reported lack of time for participation; one lost interest; one patient experienced chest pain which necessitated breaking the code, one died suddenly of a myocardial infarction, and one developed a severe respiratory tract infection.

Of the 45 subjects randomized to placebo, four dropped out prior to completing the study. One was noncompliant with both medication and follow-up visits; two reported lack of time for participation; and one patient started a new medication and feared a drug interaction.

The primary outcomes are presented in Table 2. Despite a small deterioration in mean FEV₁ in both groups (0.004 L in the ambroxol group, 0.021 L in the placebo group), and essentially stable FEF 25-75 (increase of 16 ml/s in the ambroxol group, deterioration of 123 ml/s in the placebo group), questionnaire scores improved in the major areas in which benefit with ambroxol was anticipated. This improvement was maintained over the four weeks of the trial, but was closely comparable in the two groups. There were no statistically significant differences between active and placebo, nor were there substantial trends. Results of individual questions favored placebo as often as they favored ambroxol. Confidence intervals around the differences in the two groups always overlap zero (reflecting that none of the differences are statistically significant) and are narrow, effectively excluding a large benefit for ambroxol.

Results were similar for outcomes not reported in Table 2, including other symptom questions and the daily diary. Eighteen of 36 (50 percent) patients receiving ambroxol reported overall improvement, as did 24 of 40 (60 percent) receiving placebo (p = 0.89). The 95 percent confidence interval around the difference in the proportion improved is −33 to 13 percent. Given these results, we would have required 25 subjects per group to detect a relative risk reduction of 25 percent. Thus, our results indicate that if ambroxol does yield a relative risk reduction in the proportion of patients not improved, that reduction is less than 25 percent.

Five subjects receiving ambroxol reported experiencing a bad taste in their mouth, and one each had headaches, chest tightness, and a rash. Five patients receiving placebo reported side effects. One had

Table 2—Major Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Ambroxol</th>
<th></th>
<th>Placebo</th>
<th></th>
<th>Net Benefit (Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Four Weeks</td>
<td>Net Effect</td>
<td>Baseline</td>
<td>Four Weeks</td>
</tr>
<tr>
<td>Amount of cough</td>
<td>3.62*</td>
<td>4.11</td>
<td>0.59</td>
<td>3.42</td>
<td>3.97</td>
</tr>
<tr>
<td>Inability to cough up sputum</td>
<td>3.80</td>
<td>4.23</td>
<td>0.43</td>
<td>4.04</td>
<td>4.67</td>
</tr>
<tr>
<td>Frustration over coughing</td>
<td>4.51</td>
<td>4.29</td>
<td>0.78</td>
<td>4.51</td>
<td>4.91</td>
</tr>
<tr>
<td>Cough interfering with activities</td>
<td>4.67</td>
<td>4.18</td>
<td>0.51</td>
<td>4.76</td>
<td>5.37</td>
</tr>
</tbody>
</table>

*Each symptom is rated on a scale of 1 to 7, where 1 represents worst function, and 7 represents optimal function.
†The net benefit is calculated by subtracting the difference between follow-up and baseline in the placebo group from the difference between follow-up and baseline in the ambroxol group—the number is positive when there is a trend in favor of active drug, negative when there is a trend in favor of placebo.
‡The 95 percent confidence interval around the net benefit indicates the possible range of "true" benefit.
muscle spasms, one sore legs, two swelling of the legs, and one a sensation of sputum in the throat.

**Discussion**

Ambroxol is a trans-4-[2-amino-3,5-dibromo-benzyl, amino] cyclohexanol-hydrochloride which has been shown to increase the number and activity of type 2 pneumocytes, and thus, to increase surfactant levels and lecithin/sphingomyelin ratio and mucociliary clearance in a number of animal models. Mucociliary transport and sputum viscosity have improved with ambroxol in human studies, but these effects have not been consistently replicated.

In the present study, all measures of both symptoms and pulmonary function failed to show any trend in favor of ambroxol in subjects with bronchitis with, or without, chronic airflow limitation. Given the relatively small sample size, could the study result have been false negative? The proportion of patients reporting benefit from the medication was actually 10 percent greater in the placebo group than in actively treated patients (60 and 50 percent, respectively). Confidence intervals around the difference in the proportion of patients improved is −33 to 13 percent. That is, the results are consistent with a true added benefit of 33 percent with placebo over ambroxol or a true added benefit of 13 percent with ambroxol over placebo. These results, as well as the narrow confidence intervals around symptom scores, suggest that the results exclude all but a clinically trivial benefit for ambroxol.

Ericsson et al have recently reported a double-blind RCT in which 11 of 32 placebo treated patients, 18 of 31 patients treated with 60 mg of ambroxol daily, and 20 of 32 patients treated with 120 mg of ambroxol daily, reported improved chest symptoms. The difference between the placebo and high-dose ambroxol group was statistically significant (p = 0.046). However, Ericsson et al, like our own study, showed no difference in any of the following: pulmonary function; daily diary monitoring amount, apparent viscosity, color, and difficulty expectorating sputum; end of period questionnaires concerning breathlessness and added lung sounds; and willingness to continue taking the medication. Because there were multiple measures of outcome, no statistical correction for the multiple measures was made, and the one positive finding showed a borderline level of statistical significance, it is plausible that the single positive result represents a chance finding.

The present study provides strong evidence that ambroxol is of little or no benefit in patients with chronic bronchitis who have difficulty raising sputum, irrespective of the presence or absence of airflow limitation. The placebo response rate of 60 percent in this study reinforces the need for carefully controlled trials with rigorous double-blinding in the assessment of mucolytic agents.

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