The Addition of An Aerosol Anticholinergic to An Oral Beta Agonist Plus Theophylline in Asthma and Bronchitis*

A Double-blind Single Dose Study

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In two groups of patients, 15 with asthma and 15 with chronic bronchitis, the bronchodilator effects of ipratropium bromide, of fenoterol plus theophylline, and of the combination of the three drugs, were compared using a double-blind, single-dose, placebo-controlled format. Ipratropium bromide caused rapid bronchodilatation which was not significantly different in asthmatic patients and patients with bronchitis ($\Delta$FEV$_1$ = .29 L in one hour in asthmatic patients, .18 L in patients with bronchitis). In contrast, fenoterol plus theophylline induced a considerably greater effect in asthmatic patients ($\Delta$FEV$_1$ = .41 L in one hour) than in those with bronchitis ($\Delta$FEV$_1$ = .07 in one hour). The use of the three drugs in combination compared with ipratropium bromide alone, or fenoterol plus theophylline alone, resulted in a significant additional bronchodilatation in asthmatic patients. In the patients with bronchitis, the triple combination was clearly superior to fenoterol plus theophylline. A similar trend was present in comparing the triple combination to ipratropium bromide, but the difference did not reach statistical significance. There was no evidence of synergism when ipratropium bromide was combined with fenoterol plus theophylline in that the total bronchodilator effect was approximately additive. Asthmatic patients and the physician were able to distinguish the triple combination from placebo. No such ability was demonstrated with respect to those with bronchitis. All three drugs were well tolerated. Side effects were mostly mild, and none was related to the use of ipratropium.

Several studies$^{14}$ of patients with asthma and chronic bronchitis have demonstrated a significant bronchodilator effect of the drugs ipratropium bromide (I), an aerosol anticholinergic agent, fenoterol (F), a beta-selective agonist, and theophylline (T), when the effect of each drug alone has been assessed. In most$^{47}$ but not all$^{8}$ studies, the bronchodilatation induced by a beta-agonist and theophylline in combination has been at least additive and perhaps synergistic,$^{8,10}$ and this combination is commonly employed clinically. However, the option of adding ipratropium bromide to such a regimen in patients with asthma or bronchitis has received little attention. Hence, in our placebo-controlled double-blind trial, symptomatic and ventilatory responses to I alone, a beta-agonist (F) plus T (theophylline), and the combination of the three drugs, were determined in two groups of patients with asthma and chronic bronchitis, respectively. Analysis of the results was directed particularly toward the detection of additive or synergistic bronchodilation or side effects when the three drugs were used in combination.

Methods

Patients

Thirty-six patients entered the study. Five did not complete the protocol for reasons unrelated to the drugs. One patient ingested caffeine during the test and his data were not included in the analysis. Fifteen patients with chronic bronchitis and 15 with asthma completed the protocol satisfactorily. The diagnosis of asthma or chronic bronchitis in these patients was based upon standard definitions of asthma and chronic bronchitis.$^{11}$ Patients who had any significant renal, cardiac, hepatic, or metabolic disease, glaucoma, symptomatic prostatic hypertrophy, bladder neck obstruction, or pregnancy were excluded. At the time of testing, each patient was clinically stable on an established medication regimen.

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All of the patients with asthma and 13 with bronchitis were on therapy with a beta2-agonist. In ten with asthma and two with bronchitis, the regimen included prednisone in doses not exceeding 15 mg daily. One with asthma and four with bronchitis were current cigarette smokers; these subjects did not smoke for one and a half hours prior to testing. Data for 30 patients are included; 15 of these fulfilled the criteria for asthma with no evidence of chronic bronchitis and 15 had chronic bronchitis with no evidence of asthma or atopy. Their ages ranged from 17 to 72, mean 54. (The mean age of the asthmatic subjects was 52.3, and of those with bronchitis, 59.9 years). Eleven patients were classified by a physician as "severe," 14 "moderate," and five "mild," with regard to their clinical condition. Duration of disease ranged from three to 59 years with a mean of 16 years.

**Trial Design**

Patients were brought fasting to the laboratory on each of four separate days and had had no bronchodilator medication for at least 12 hours. On each of the days a different combination of bronchodilators was given according to a randomized, double-blind protocol. The four different combinations were:

- **P** = Three placebos (two oral, plus one aerosol).
- **F + T** = F, 5 mg and T (oxtriphylline, 400 mg equivalent to 250 mg theophylline), oral, plus placebo aerosol.
- **I** = Two oral placebos plus I, 40 mg aerosol.
- **F + T + I** = F, 5 mg oral and T, 400 mg oral plus I, 40 mg aerosol.

The patients were assessed before, and 30 minutes, one hour, two hours, and three hours, after administration of the drugs. Spirometry was performed with measurement of forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and forced expiratory fraction at 25 percent to 75 percent of vital capacity (FEF25-75)—reflecting the best of three comparable efforts at each assessment period. At each assessment period, respiratory symptoms and side effects were evaluated by questionnaire. Patient and physician overall evaluation was recorded at three hours.

**Statistical Methods**

The factors present in the design were patient disorder (asthma vs bronchitis), drug treatment (placebo, I, F + T, I + F + T), and time after administration (0, 1, 2, and 3 hours). Thus, the overall design was a $2 \times 4 \times 4$ factorial with repeated measures over the 16 combinations of drug treatment by time for each of 15 subjects with asthma and 15 with bronchitis. Analysis of variance for this repeated measures design was performed on changes from baseline (during each treatment episode) of pulmonary function indices, blood pressure, and heart rate. Since these global analyses indicated different patterns of response to drug treatments in asthma and bronchitis, patient disorders by drug treatment interaction ($p < 0.005$), and greater response variation in asthmatics, separate analyses of variance for repeated measures was performed for the asthma and bronchitis patients. In both the global and separate analyses, pairs of treatment means were tested for significance using the appropriate within or between patient estimates of standard errors from the relevant analysis of variance. Tukey's method was used to reduce the effect of the multiplicity of such tests on the overall error rate.

The four-drug treatment combinations themselves possess a $2 \times 2$ factorial treatment structure (1 present or absent vs F + T present or absent). This allowed examination of the separate effects of I and F + T and any interaction between their effects using data from all four drug treatment combinations. The interaction effect measured the degree of synergism or antagonism in the combination of I with F + T. The separate and interaction effects on indices of pulmonary function were estimated at each time after administration of the drug treatments. Standard errors for testing the significance of these estimated effects were derived from error terms in two-way analysis of variance (patient by drug treatment) on the responses at each time for the patients with bronchitis and asthma.

The patient and physician assessments of clinical symptomatology were analyzed using an exact small sample version of McNemar's test. This was done by classifying the patients' (or physician's) responses (no effect or some effect) into a two-way table for each pair of drug treatments. A similar method was used to analyze the difference in observed side effects with F + T and I + F + T. For this analysis, patients were classified as exhibiting no side effects or one or more side effects after receiving F + T or I + F + T.

**RESULTS**

**Ventilatory Function**

Figure 1 illustrates the time course of the FEV1 for four treatment groups ± standard error of the mean.
response. Over the three hours of study, placebos alone produced no significant changes from baseline. Furthermore, there were no significant differences in the placebo response between the asthma and bronchitis groups, although compared with baseline, there was a nonsignificant trend toward lower values of FEV₁ in the asthma patients than in those with bronchitis, during the placebo trial.

In both asthma and bronchitis patients, I alone elicited a rapid increase in FEV₁ maximal within an hour. There was no significant difference in the effect of I on FEV₁, in patients with asthma (0.29 L at one hour), versus bronchitis (0.18 L at one hour) (Table 1). In both groups, the response to F + T alone was slower in the first half hour, but continued to increase up to three hours. The increment in FEV₁ following F + T, in contrast to that following I, was considerably greater in the asthma group (maximum FEV₁ increase, 0.47 L) than in the bronchitis group (maximum FEV₁ increase, 0.17 L) (Fig 1). Nevertheless, even in the bronchitis group the effect of F + T was significant at all times (Table 1).

In the bronchitis group, the response to I averaged over the three hours was greater than that of F + T alone (p < .05, Fig 1), although at three hours the FEV₁ response to F + T had not yet plateaued. In the patients with asthma, a similar difference in the time course of response was seen, but the magnitude of the response to F + T greatly exceeded that of the response to I (Fig 1). The changes in FVC were similar to changes in FEV₁ in both groups.

The use of the three drugs in combination produced the greatest increase in FEV₁ and FVC. In the group with asthma, the FEV₁ response to the combination at two and three hours (Fig 1) significantly exceeded that of both F + T alone (p < 0.05) and I alone (p < 0.01). In the bronchitis group, however, the mean increment induced by the combination was significantly (p < 0.05) greater than that of F + T alone, but not greater than that of I alone (p > 0.05).

In both groups the possibility of interactive (synergistic) effects of the drugs was assessed by analysis of variance of the FEV₁ or FVC response at each time. There was no evidence of an interactive effect of the drugs in either patient group at any time period. The results of all such analyses are summarized in Table 1. In each patient group, a significant direct effect of I and of F + T combination was found at all time intervals (p < 0.01 or better) with the exception of the oral F + T at 1/2 hour.

**Clinical Assessment**

Table 2 summarizes the patients' subjective assessments and the physician's global evaluations of benefit of the four drug regimens in the two disease categories. In patients with asthma, the physician was able to distinguish both I alone (p = .03) and the combination of I with F + T (p = .02) from the placebo. The asthma patients themselves were able to distinguish only the combination of I with F + T from placebo (p = .004). In the patients with bronchitis neither the patient nor the physician could distinguish any combination from placebo.

### Table 1—Effects of I, F + T, and Their Interaction upon Change in FEV₁

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Asthma</th>
<th>Bronchitis</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F+T</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>1/2</td>
<td>.179†</td>
<td>.261†</td>
<td>NS</td>
</tr>
<tr>
<td>1</td>
<td>.407†</td>
<td>.287†</td>
<td>NS</td>
</tr>
<tr>
<td>2</td>
<td>.503†</td>
<td>.245†</td>
<td>NS</td>
</tr>
<tr>
<td>3</td>
<td>.580†</td>
<td>.230†</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F+T</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>1/2</td>
<td>.035*</td>
<td>.147†</td>
<td>NS</td>
</tr>
<tr>
<td>1</td>
<td>.070†</td>
<td>.182‡</td>
<td>NS</td>
</tr>
<tr>
<td>2</td>
<td>.107†</td>
<td>.167†</td>
<td>NS</td>
</tr>
<tr>
<td>3</td>
<td>.005†</td>
<td>.126‡</td>
<td>NS</td>
</tr>
</tbody>
</table>

* < p 0.05; † < p 0.01; ‡ < p 0.001

### Table 2—Patients' Subjective Assessment of Benefit, by Questionnaire, and Physician's Evaluation of Clinical Benefit, Asthma and (Bronchitis)

<table>
<thead>
<tr>
<th></th>
<th>Helped Breathing</th>
<th>A little</th>
<th>A lot</th>
</tr>
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<tr>
<td>Patients' assessment</td>
<td>Not at all</td>
<td>A little</td>
<td>A lot</td>
</tr>
<tr>
<td>Placebo</td>
<td>9 (9)</td>
<td>1 (4)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Ipratropium</td>
<td>7 (4)</td>
<td>3 (5)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Fenoterol and Theophylline</td>
<td>7 (5)</td>
<td>5 (4)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Ipratropium and Fenoterol plus Theophylline</td>
<td>8 (1)</td>
<td>2 (8)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Physician's assessment</td>
<td>Not at all</td>
<td>A little</td>
<td>A lot</td>
</tr>
<tr>
<td>Placebo</td>
<td>11 (9)</td>
<td>3 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Ipratropium</td>
<td>8 (4)</td>
<td>4 (7)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Fenoterol plus Theophylline</td>
<td>8 (6)</td>
<td>5 (4)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Ipratropium and Fenoterol plus Theophylline</td>
<td>7 (2)</td>
<td>6 (7)</td>
<td>2 (6)</td>
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Table 3—Side Effects (Asthmatic plus bronchitis patients)

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>I</th>
<th>F + T</th>
<th>I, F + T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Irritability</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Palpitations</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Shakiness</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Heartburn</td>
<td>4</td>
<td>2</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Total episodes</td>
<td>3</td>
<td>1</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Severity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A lot</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>A little</td>
<td>3</td>
<td>2</td>
<td>10</td>
<td>17</td>
</tr>
</tbody>
</table>

Side Effects

The patients' responses to the questionnaire concerning side effects are tabulated in Table 3. In general, the drugs were well tolerated—no one withdrew or complained spontaneously of any symptoms. A paired analysis (pairing the results for each patient) showed that the number of patents suffering from one or more side effects did not differ under F + T (four patients) and I + F + T (nine patients), (two sided p = .27).

Pulse Rate, Blood Pressure

The overall effect of F + T was to increase pulse rates in both asthma and bronchitis patients (p < 0.001). By three hours, the mean rise compared to placebo was significant in both groups (p < .05) (Fig 2). In response to I alone the pulse rate tended to decrease, but was never significantly different from placebo at any time for either group.

The pulse rate response to the combination I + F + T was not significantly different from that to F + T alone at any time for the two groups.

There were no significant effects of I or F + T on systolic blood pressure. However, administration of F + T, but not I, produced a drop in diastolic blood pressure, in asthma patients (4.8 mm Hg, p < .001), and bronchitis patients (2.6 mm Hg, p < .05).

Discussion

There is ample documentation that I induces a dose-dependent bronchodilatation in asthmatic as well as bronchitis patients. Furthermore, it has been shown that I adds to the effect of F alone or T alone. On the other hand the additional bronchodilatation achieved by the use of a beta agonist and a theophylline derivative in combination is well documented and the use of this combination in a bronchodilator regimen is thus a common clinical strategem.

To our knowledge, only one previous study of 13 asthmatic patients has examined the effect of adding I to a theophylline plus a beta agonist. In this study, the three-drug combination produced the greatest increments in FEV1. In the present study we compared the response to I of patients with asthma or bronchitis who in addition received a conventional dose of a beta agonist (F) and oral theophylline (T). We used a single-dose format administering the various drug combinations randomly on successive days according to a double-blind protocol.

Figure 2. Average heart rates for patients with asthma over three hours, for the treatment and placebo groups.
Using standard ventilatory parameters of airway patency, we confirmed the significant bronchodilator effect of I alone, and found that the increase in FEV₁ was of similar magnitude in the subjects with asthma or bronchitis, in contrast to the F + T combination which induced a much greater bronchodilation in those with the asthma than in those with bronchitis. Previous studies have reported similar findings. In addition, however, we found that in both groups I added significantly to the bronchodilation induced by the combination of F + T, although in subjects with bronchitis the converse was not true, that is, F + T failed to add significantly to the bronchodilation induced by I. The rapid onset of I effect, and the likelihood of continued activity of F + T beyond the three-hour period of measurement presumably reflected the different routes of administration.

In order to examine further the interactive effects of I and F + T we subjected the results at each time point to two-way analysis of variance. The lack of a significant interactive effect (the total bronchodilation induced by the three-drug combination being very close to the sum of that induced by the drugs when used separately) suggested that the action of I was independent of that of F + T.

The clear-cut bronchodilatation revealed by measurement of ventilatory parameters was not readily apparent to either the patients or the examining physicians. In the asthmatic patients only the three-drug combination was distinguished from placebo by both the patients and the physician, and even this combination was not distinguished from placebo by the bronchitis patients or the physician. The lack of significant response to placebo, the consistent trend in the ventilatory results, and the demonstration of significance by analysis of variance as well as paired analysis indicated that the ventilatory measurements were a valid reflection of an increased airway patency which was not identified by the subjects or by the physician’s clinical assessment.

Given that the addition of I offered bronchodilatation beyond that achieved by a standard dose of F + T, it was important to examine whether the triple combination was associated with additional side effects. In fact, we found that although increased positive responses to the side effects questionnaire were obtained, these were largely of minor severity (“a little” as opposed to “a lot”), and indeed the difference in number of patients having any side effects with F + T only compared with those having side effects with I + F + T only was not statistically significant.

The use of I alone and in combination with F + T was not associated with a significantly increased incidence of side effects. The addition of I to a bronchodilator regimen employing a beta₂ agonist and theophylline may result in clinically useful additional bronchodilatation in patients with chronic bronchitis and in those with asthma.

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