Efficacy of Inhaled Metaproterenol and Orally-administered Theophylline in Patients with Chronic Airflow Obstruction*

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To evaluate comparative bronchodilator efficacy with chronic airflow obstruction (CAO), we randomly administered to ten patients week-long treatments consisting of: (1) inhaled metaproterenol from a metered dose canister (1.30 mg six times a day) and doses of a sustained-release theophylline formulation sufficient to achieve plasma levels of 10-15 μg/ml; (2) metaproterenol-placebo; (3) theophylline-placebo; or (4) placebo-placebo. At the end of each period, treatment responses were evaluated by spirometric tests, by exercise tolerance (12 minute walk and progressive cycle ergometry) and by subjective perception of dyspnea (oxygen cost diagram and breathlessness rating). Metaproterenol as a single treatment caused statistically significant improvements in spirometric variables and in the breathlessness rating. Theophylline as a single treatment caused significant changes in none of the test variables, though favorable trends were observed. Combined drug therapy was significantly better than metaproterenol only in the case of the breathlessness rating. We conclude that in the treatment of patients with CAO, inhaled metaproterenol is superior to oral theophylline. Our results permit no definite conclusion concerning added benefits of combined drug therapy.

Optimal bronchodilator treatment of chronic airflow obstruction (CAO) remains a subject of controversy. Both inhaled beta-adrenergic agonists and oral theophylline formulations induce modest bronchodilation in most patients with CAO, and both classes of drugs, singly or in combination, are widely prescribed for treatment.14 Despite their common use in CAO there exists very little information about comparative efficacy. This is not a trivial question. Unlike the inhaled beta-agonists, theophylline prescribing is complex and its use may be associated with serious toxicity.5,7

We undertook the present study to compare the relative efficacy of an inhaled beta agonist, metaproterenol, and a sustained-release theophylline preparation, each drug given singly or in combination. At the end of week-long treatment periods, we compared ventilatory function, exercise tolerance, and subjective indices of breathlessness.

**Material and Methods**

**Patient Selection**

We identified male patients, age 40-70 years, from an outpatient clinic with a history of slowly progressive dyspnea on exertion, with a forced expiratory volume in one second (FEV1) of less than 1.5 L and with a ratio of the FEV1 to the forced vital capacity (FVC) of less than 60 percent. We excluded patients with significant chest roentgenographic abnormalities not consistent with CAO alone. We also excluded patients suspected of having asthma by one or more of these criteria: (1) history of atopy; (2) sputum or blood eosinophilia; (3) absence of long-term cigarette usage; (4) frequent, episodic attacks of wheeziness; (5) regular use of corticosteroids; and (6) FEV1 response to an inhaled beta agonist of greater than 25 percent of baseline. Patients were also excluded from study if they had coexisting disease which might interfere with exercise testing.

**Test Methods**

The forced vital capacity (FVC) and FEV1 were measured with a wedge spirometer (model 570, Med Sciences Electronics, Inc, St. Louis, MO). Exercise performance was evaluated with the 12 minute walk (12 MW) and with progressive cycle ergometry (PCE).8 The 12 MW was performed on a level hospital corridor with the patients instructed to walk as far as they were able, at a pace of their choosing, within the 12 minute period. PCE was begun at a workload of 200 kpm/min which was increased in 200 kpm/min increments at one-minute intervals. Test performance was measured as the time to exhaustion. Subjective breathlessness was assessed with the oxygen cost diagram (OCD) and the breathlessness rating (BR).6 On the OCD, everyday activities are positioned along a 100 mm vertical scale proportional to the oxygen cost of specific activities. Subjects place a mark at that point which best corresponds to their work capabilities during that test period. The BR diagram is a similar analog scale marked off in 10 mm divisions, 0 mm representing the patient's most breathless state and 100 mm the least breathless state. Plasma theophylline concentrations were measured with an enzyme immunoassay (Emit-AAD, Syva, Palo Alto, CA).

**Study Design**

Subjects were studied over a five-week period. During the first week, each subject was thoroughly familiarized with all test procedures. For the last four weeks, subjects were assigned to treatments according to a double-blind, randomized block design. Each one-week treatment consisted of one of the following:

1. Metaproterenol-theophylline: Two inhalations (each supplying 0.65 mg) of metaproterenol from a metered-dose canister (Alupent, Boehringer-Ingelheim) every three hours while awake (7:00 AM-10:00 PM) and sustained-release anhydrous theophylline tablets (Theo-Dur, Key Pharmaceuticals) given twice daily (7:00 AM and 7:00 PM) in amounts to provide average plasma concentrations of 10-15 μg/ml.

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CHEST / 89 / 2 / FEBRUARY, 1986 171


2. Metaproterenol-placebo: Metaproterenol as given in (1) and placebo tablets identical in number and appearance to the theophylline tablets in (1).

3. Placebo-theophylline: Inhalations from a metered-dose canister containing all but the active drug as in (1) and sustained-release theophylline as in (1).

4. Placebo-placebo: Placebo metered dose canister and placebo tablets.

Patients reported to the laboratory at 8:00 AM on the final two days of each treatment period. All tests were performed within one to two hours after the last doses of medication. On both days, spirometric testing was performed and the analog breathlessness scores obtained. Reported results represent the mean of values from the two days. On the first day patients performed the 12 MW twice, separated by 30 minutes, and the longer of the two distances was used for analysis. On the second day, PCE was performed on a single occasion. Blood for theophylline determination was drawn at 8:00 AM on the first day of testing (one hour after their last dose). On both days resting blood pressures and pulse rates were measured and the patients were questioned concerning adverse effects.

Statistical Analyses

Possible differences among treatment results were assessed by repeated measures analysis of variance with the Greenhouse Geisser adjustment. Where this indicated that significant (p < .05) differences existed, comparisons between treatments were made with the Student's t test for paired data. The Bonferroni adjustment was made for multiple comparisons, and differences were considered significant for p < .01.

RESULTS

Ten patients (mean age 61 years, range 53-72 years) were admitted to the study and all successfully completed it. None reported any adverse side effects from any of the treatments, though pulse rates during both theophylline-containing treatments were increased on average by 11 percent. There was no significant effect of any treatment upon blood pressure. Theophylline levels measured at day 6 of each period were 11.6±1 µg/ml for the placebo-theophylline treatment and 12.8±1.3 µg/ml for the metaproterenol-theophylline treatment.

The mean and range of all other measured variables for each treatment regimen are given in Table 1. Metaproterenol as a single treatment (M-P) resulted in significant improvement in the FVC, in the FEV₁₀, and in the BR when compared to the P-P treatment.

Theophylline treatment alone (P-T) was not significantly different from P-P treatment for any of the test results. The combination of metaproterenol and theophylline caused significant improvement in the FVC, in the OCD, in the BR, and in the 12 MW. Only with regard to the BR did the combined treatment with metaproterenol and theophylline cause significant improvements over single treatments.

DISCUSSION

The absolute magnitude of bronchodilator-induced changes for all treatments and for all test parameters are modest, as might have been predicted from the characteristics of our study population. Given these small changes and the size of the study group, conclusions about relative treatment efficacy must be circumstantial. Based upon our findings, we believe it is fair to conclude that in the doses administered, inhaled metaproterenol is as (or more) effective as theophylline regardless of whether judgments of efficacy are based upon ventilatory function, symptom scores, or exercise tolerance. Although our test results suggest that combined treatment may be more efficacious than either single treatment, differences are statistically significant for only one result, and we believe that definitive conclusions concerning advantages of combined therapy are unwarranted.

The doses of metaproterenol and theophylline administered in this study may not be those which are maximally effective. Bronchodilator responses to theophylline in CAO are dose-dependent in the usual therapeutic range (10-20 µg/ml) and the maximally-effective dose may be indeterminant because of associated systemic toxicity. Theophylline doses sufficient to cause low therapeutic levels were deliberately administered in this study because we wished to minimize side-effects. Higher levels might well have produced more clearcut beneficial effects, but in the clinical setting higher levels will necessarily be associated with greater risk of serious toxicity. As will be discussed below, we believe that a rational judgment about the use of theophylline rests heavily upon the

Table 1—Mean and Range of Values for Spirometry, Symptom Scores and Exercise Tolerance for Each Treatment

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Metaproterenol</th>
<th>Placebo</th>
<th>Metaproterenol</th>
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<tr>
<td></td>
<td>Theophylline</td>
<td></td>
<td>Theophylline</td>
<td></td>
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<tr>
<td>FVC (L)</td>
<td>2.63</td>
<td>2.92*</td>
<td>2.78</td>
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<tr>
<td>(1.69-3.74)</td>
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<td>(2.01-4.11)</td>
<td>(1.95-4.01)</td>
<td>(2.02-3.89)</td>
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<td>FEV₁₀ (L)</td>
<td>0.65</td>
<td>0.77*</td>
<td>0.73</td>
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<td>(0.25-1.05)</td>
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<td>(0.29-1.33)</td>
<td>(0.59-1.16)</td>
<td>(0.35-1.15)</td>
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<td>OCD (mm)</td>
<td>51.3</td>
<td>57.7</td>
<td>58.8</td>
<td>62.0*</td>
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<td>(23.6-86.9)</td>
<td></td>
<td>(32.3-88.3)</td>
<td>(39.4-85.0)</td>
<td>(39.8-84.5)</td>
</tr>
<tr>
<td>BR (mm)</td>
<td>53.3</td>
<td>56.7*</td>
<td>63.6**</td>
<td>63.8**</td>
</tr>
<tr>
<td>(25.3-86.2)</td>
<td></td>
<td>(37.6-87.2)</td>
<td>(30.0-84.8)</td>
<td>(43.9-86.0)</td>
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<td>12MW (m)</td>
<td>764</td>
<td>802</td>
<td>796</td>
<td>829*</td>
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<td>(546-950)</td>
<td></td>
<td>(653-959)</td>
<td>(615-984)</td>
<td>(685-1003)</td>
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<td>PCE (min)</td>
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<td>(2.8-8.3)</td>
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<td>(2.7-7.0)</td>
<td>(2.8-6.6)</td>
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</tr>
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</table>

*p<.01 compared to placebo-placebo
*p<.01 compared to metaproterenol-placebo
*p<.01 compared to placebo-theophylline

Metaproterenol and Theophylline in Chronic Airflow Obstruction (Dullinger, Kronenberg, Niewehner)
expected risk-to-benefit ratio.

Metaproterenol was administered in maximally-recommended doses, but these may not be maximally-effective. The patients in our study were given no special instructions concerning the spacing of the two puffs of metaproterenol which comprised each treatment. The sequential inhalation of single puffs of a beta agonist at intervals of several minutes may be more effective than the same doses given at close intervals.18 Barclay and associates19 administered salbutamol to patients with CAO at hourly intervals and found the maximally effective dose to be variable, but it exceeded the usual recommended dose by a several-fold factor in most patients. These larger doses of salbutamol were without evident systemic effects, and when theophylline was added to the maximally-effective dose of salbutamol, only a minority of subjects experienced further bronchodilation.

The present study was designed to closely simulate clinical prescribing conditions and we believe the findings have direct relevance to patient treatment. We have shown that regular use of metaproterenol from a metered dose inhaler does produce bronchodilation and that these increases in ventilatory function are related to some measurable improvement in symptoms. The benefits of this therapy, while modest, are associated with few disadvantages. Some patients find use of the inhaler less convenient than taking tablets and a few have difficulty in coordinating the delivery system to ensure adequate drug deposition.14 Treatment with inhaled beta agonists from metered-dose inhalation is devoid of systemic effects even when recommended doses are exceeded by a wide margin.2,3,13

We were unable, in this study, to demonstrate that theophylline caused statistically significant improvement in any test parameter, a result which may be due in part to the small number of patients studied. Our own work and that of others indicates that theophylline does induce modest increases in ventilatory function which are correlated with some amelioration of symptoms.6-18 Balanced against these benefits are the complexities of achieving therapeutic plasma levels and the dangers of serious toxicity. Reliable estimates as to the overall incidence of serious toxicity are not available, but published reports and our experience indicate that the problem is not uncommon.6,7

Consideration of relative benefits and risks clearly favors the use of an inhaled beta agonist over theophylline as single agent therapy for CAO. It remains unclear whether both an inhaled beta agonist and theophylline should be routinely prescribed for patients with characteristics of those in this study. Our data suggest that the combined treatments may be superior to single agents and these findings are consistent with others in the literature.10,16,17 However, it bears emphasizing that the further advantages of combination treatment, if present, are small and that they might be further reduced with more vigorous inhaled beta-agonist therapy.9 In this patient population, the complexities and risks of theophylline may outweigh the benefits. The same may not apply to those patients with more bronchodilator-responsive disease.

ACKNOWLEDGMENTS: This study was supported by Veterans Administration Research Service.

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