The Effects of Oral Doses of Theophylline and Fenoterol on Exercise-Induced Asthma*

Peyton A. Eggleston, M.D.; Patsy P. Beasley, R.N.; and Robert T. Kindley, M.D.

The effects of oral doses of theophylline and a β-adrenergic agonist, fenoterol, were examined in 18 asthmatic young adults. Significant bronchodilation was seen with high-dose theophylline (FEV₁ increased 14 percent) and with full 10-mg doses of fenoterol (FEV₁ increased 10 percent). Low-dose theophylline alone (130 mg) increased FEV₁ by 5 percent, but when combined with 5 mg of fenoterol, a 14 percent improvement was seen, demonstrating significant (P=.003) additive effects. The ability of the two drugs to prevent the asthmatic response to exercise was not additive. The mean fall in FEV₁ was not statistically different when subjects exercised after receiving a placebo (32 percent) 130 mg of theophylline (27 percent), or 130 mg of theophylline with 5 mg of fenoterol (18 percent). Furthermore, side effects associated with the two drugs, such as tachycardia, tremor, or CNS stimulation, were significantly increased when the two drugs were given simultaneously. Thus, little therapeutic benefit was gained from simultaneous therapy. Both bronchodilation and toxicity were equivalent to that seen with larger therapeutic doses of either drug given alone, and protection from the effects of a frequently encountered stress was not significantly enhanced.

As bronchodilators, theophylline and β-adrenergic agonists appear to have partially additive effects. Pulmonary function improves to a greater extent when the two drugs are given together than when the same doses are given separately.1-5 In vivo effects are not synergistic, as might be predicted from in vitro studies demonstrating that both agents act to increase intracellular cyclic AMP,4 and that their effects on both cyclic AMP and cellular function are synergistic.4-6

In addition to their effects as bronchodilators, the therapeutic usefulness of β-adrenergic agonists and methylxanthines also depends on their ability to prevent attacks of asthma induced by a variety of stimuli. Asthmatic patients, because of their characteristic bronchial irritability, repeatedly have brief episodes of increased obstruction on encountering a variety of unavoidable stimuli, such as physical activity,7, cold air,4 pollutants,6 and allergens.10 In the context of their demonstrated ability to diminish the asthmatic patient's characteristic hyperirritability, β-adrenergic agonists and methylxanthines act as modulators rather than bronchodilators.

For any asthmatic drug, bronchodilation and modulation of induced attacks may be distinct effects, as was first suggested by the clinical effectiveness of cromolyn sodium, a drug with no bronchodilating effects.11 For β-adrenergic agonists specifically, higher doses seem to be necessary to modulate induced attacks than to produce significant bronchodilation.12-14

The present study was conducted to examine the effects of a β-adrenergic agonist (fenoterol) and of theophylline both as bronchodilators and as modulators, and to determine whether their effects in preventing exercise-induced asthma are additive.

Materials and Methods

Subjects

Twenty subjects, aged 17 to 32 years, were studied. All had asthma as defined by the American Thoracic Society,16 and seven required regular medication for control of their disease. All had a history of asthma following exercise, and before entry into the study all demonstrated a 20 percent fall in FEV₁ after exercise. All subjects gave written, informed consent.

Subject Preparation

Before entry into the experiment, each subject had a history and physical examination. Blood was obtained for blood chemistries and hemogram, and urinalysis and ECG were performed. No abnormalities were detected.

Each subject received a theophylline dose titrated to produce serum levels greater than 10 μg/ml at two hours. A dose of 8 mg/kg of anhydrous theophylline solution was first administered. If the serum concentration measured two hours later by high-pressure liquid chromatography14 was not more than 10 μg/ml, the test dose was appropriately adjusted for use in the study.

Subjects excluded methylxanthines for eight hours before...
exercise testing and for 12 hours in the case of sustained-action formulation. Adrenergic agonists were excluded for 24 hours. Subjects taking corticosteroids every other day were tested on days off medication. Anyone who was wheezing was asked to return on another day for testing.

Exercise Testing

The response to exercise was measured according to a previously described protocol. Subjects exercised on a treadmill for five to six minutes, starting from a walk. Heart rate was monitored continuously, and exercise conditions were adjusted to increase heart rate to 90 percent of the age-predicted maximum, which was then maintained for five to six minutes. Forced vital capacity (FVC), one-second forced expiratory volume (FEV1), and forced expiratory flow from 25 to 75 percent of vital capacity (FEF25-75) were determined on a water-sealed, 9-L spirometer (Warren E. Collins, Inc) before exercise and at 1, 5, 10, 15, and 20 minutes after exercise. Values were compared with published normal values.

Each subject’s response to exercise was determined six times before entering the drug-testing protocol, in order to practice the procedures and to determine the reproducibility of their asthmatic response. Treadmill speed and inclination were varied during these runs to achieve maximal heart rates in the target range. Once optimal conditions were determined, they were maintained during drug testing. Many of the subjects’ responses to exercise had been measured within the previous three months. In those for whom this was not true, further runs were performed for evaluation.

Drug Testing

Fenoterol is the 4-hydroxyphenyl derivative of metaproterenol. It is well absorbed orally, is effective for four to six hours, and has more potent bronchial effects than the parent compound. Selectivity for β-2 receptors is less than that seen with terbutaline and salbutamol, but greater than that with isoproterenol and metaproterenol.

The test drugs were supplied as fenoterol, 2.5-mg tablets, with matching placebo tablets, and as anhydrous theophylline solution containing 225 mg/30 ml with an identical solution without theophylline for a placebo (kindly supplied by Knoll Pharmaceutical Co.). A liquid theophylline preparation was tested because greater dosage flexibility was possible.

Medications were administered in a randomized order in a double-blind, six-way crossover protocol. On each of the six test days, subjects received four tablets and the volume of liquid determined on the theophylline titration test day. The number of active fenoterol tablets, and the proportions of active and placebo theophylline solutions were varied to produce the doses listed in Table 1. Each treatment was separated by a washout period of at least 24 hours.

On testing days, two spirometers were recorded, pulse rate was measured, and a test medication administered. Two hours later, spirometry and pulse were remeasured and serum was obtained for theophylline determination. The subject then performed an exercise challenge at a rate and inclination identical to those established during the standardization period and with pulse rate and spirometers measured as before.

Statistics

Results were analyzed by Student’s t test unless otherwise stated.

RESULTS

On the theophylline titration day, serum theophylline levels ranged from 10.2 to 18.2 μg/ml, with a mean of 13.3 ± 2.1 μg/ml. These levels were produced by doses ranging from 270 to 697 mg (3.5 to 10.4 mg/kg). When these doses were repeated during the experiment, the mean blood level was almost identical, 13.3 ± 3.3 μg/ml.

The lower theophylline dose, 130 mg, was administered on three testing days (on two of these days with fenoterol). Mean serum levels averaged 6.1, 5.9, and 6.0 μg/ml, respectively, approximately one half the levels following high doses of theophylline. Following administration of 10 mg fenoterol and placebo, serum theophylline concentrations averaged 2.6 and 2.9 μg/ml, respectively.

On the two test days when test medications contained no theophylline, two subjects were found to have unusually high theophylline levels (11.3 and 12.5 μg/ml). Since these subjects used moderate doses of theophylline regularly to treat their asthma, and since their theophylline levels were also unusually high on other test days, it was assumed that theophylline clearance was slower in these subjects, and their data were excluded from subsequent analysis.

For the remaining 18 subjects, baseline pulmonary function before treatment on the six test days was similar. The mean values of FVC on the six days were identical (87 percent of predicted normal values) as were the mean FEV1 values (91 percent of predicted). The mean values of FEF25-75 varied from 69 percent to 75 percent of predicted, but the values were not significantly different (P > 0.10; analysis of variance).

Bronchodilation

Bronchodilation occurred following administration of all active medications as compared with placebo (Fig 1; Table 2). Improvement was most
marked after fenoterol, 10 mg; FEV₁ increased .48 ± .09 L (12 percent of predicted normal values and 14 percent above baseline values). Following administration of the higher dose of theophylline, FEV₁ increased .35 ± .06 L (9 percent of predicted and 10.5 percent above baseline).

The effects of theophylline and fenoterol were additive. Following 130 mg of theophylline alone, FEV₁ increased only 0.16 ± .06 L (4 percent of predicted, 4.5 percent above baseline), as would be expected with the substantially lower serum levels. When a quarter dose of fenoterol was added, ie, 130 mg of theophylline and 2.5 mg of fenoterol, bronchodilation was somewhat greater. The FEV₁ increased 0.26 ± .08 L (8.2 percent of predicted and 10 percent above baseline); the enhancement beyond theophylline alone approached statistical significance (P = .07). When 5 mg of fenoterol was added to 130 mg of theophylline, bronchodilation was significantly enhanced and was not significantly different from that seen with either theophylline or fenoterol given in full doses (P > .1).

Table 2—Bronchodilation: Statistical Comparison of Data in Figure 1

<table>
<thead>
<tr>
<th></th>
<th>FEV₁</th>
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<tr>
<td>T₁₀</td>
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<tr>
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<tr>
<td></td>
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<td>NS</td>
</tr>
<tr>
<td></td>
<td>.031</td>
<td>NS</td>
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</table>

*P values derived from paired t test; N = 18.
†NS; P > .05.

Figure 2. Changes in pulmonary function from values just before exercise (2 hours after medications) to lowest values after exercise for 18 subjects. Values expressed as percentage of predicted normal (17), and brackets drawn at 1 SE.
Changes in FEF25-75 were similar to, but slightly greater than those in FEV1.

Exercise-Induced Asthma

Exercise response is shown in Figure 2 and is compared statistically in Table 3. Maximal pulmonary function changes after exercise are compared with post-drug values, as well as being expressed as a percentage of predicted norms.

The modulating effects on exercise-induced asthma were not so clear as was bronchodilation. Only high-dose theophylline and 10 mg of fenoterol significantly inhibited exercise-induced asthma. On the day placebo was given, mean FEV1 two hours after dosing (i.e., post-drug value) was 3.54 L and fell to 2.37 L following exercise; thus, there was an exercise-induced decrease of 1.17 L (27 percent of predicted normal FEV1 values, 32 percent of post-drug values). On the day high-dose theophylline was administered, FEV1 decreased by .64 ± .09 L after exercise (17 percent of predicted, 17 percent of post-drug values), and on the day 10 mg of fenoterol was administered, FEV1 decreased by .56 ± .08 L following exercise (14 percent of predicted values, 15 percent of post-drug values). These changes were significantly less than those following placebo (Table 3). Furthermore, they are similar to those seen with nonasthmatic patients exercised according to the conditions outlined.7

While there was a suggestion of additive inhibition of exercise-induced asthma by combinations of lower doses of fenoterol and theophylline, the changes were not statistically significant. As shown in Figure 2, exercise-induced changes in FEV1 following theophylline, 130 mg (1.02 ± .13 L; 27 percent of predicted values, 27 percent of post-drug values), were almost identical to those following placebo. Following 130 mg of theophylline with 5 mg of fenoterol, FEV1 fell .79 ± .19 L after exercise (21 percent of predicted values, 18 percent of post-drug values); this change was not significantly different from that seen following either placebo (P = .07) or 130 mg of theophylline alone (P = .13).

None of the treatments significantly inhibited FEF25-75 changes when compared with placebo, although high-dose theophylline was effective when compared with 130 mg of theophylline (P = .03).

The net effects of bronchodilation and modulation of exercise-induced asthma are summarized in Figure 3. Comparing FEV1 values before exercise with the lowest values after exercise showed that all active drugs had some effect on the net change. Following the three most effective regimens, the net change was only 2 percent (10 mg of fenoterol), 8 percent (high-dose theophylline), and 7 percent (130 mg of theophylline with 5 mg of fenoterol). It is apparent, however, that these effects were largely related to bronchodilation.

The seven subjects with more severe asthma, who required daily medication to control symptoms, more clearly benefited from active drugs. For instance, FEV1 increased 16 percent following 10 mg

![Image](http://journal.publications.chestnet.org/pdffile/21206/21206_3.png)
of fenoterol and 12 percent following high-dose theophylline, but decreased 3 percent following placebo. Additive effects were still demonstrable in that the 16 percent increase in FEV₁ seen following 130 mg of theophylline with 5 mg of fenoterol was significantly greater than either the 6 percent response to 130 mg of theophylline or the placebo response (P < .05).

Additive effects on exercise-induced asthma could also be demonstrated in this group. The exercise-induced reduction in FEV₁ following 10 mg of fenoterol (11 percent), high-dose theophylline (19 percent), 130 mg of theophylline (33 percent), 130 mg of theophylline with 2.5 mg of fenoterol (28 percent), and 130 mg of theophylline with 5 mg of fenoterol (16 percent) were all significantly less than that seen following placebo (44 percent). The response following 130 mg of theophylline with 5 mg of fenoterol was significantly less than following 130 mg of theophylline alone (P < .05).

Adverse Reactions

Adverse reactions seen during the study are shown in Table 4. Ten mg of fenoterol was associated with side effects in more subjects (15 of 18) and with the greatest number of side effects (35 reports). Fewer side effects were seen following high-dose theophylline (21 reports) and following the combination of 130 mg of theophylline with 2.5 mg of fenoterol (21 reports) or with 5 mg of fenoterol (23 reports). Thus, all effective treatments were associated with side effects, and the combination of low doses of theophylline and fenoterol were associated with side effects just as frequently as was full-dose theophylline.

The reported side effects were also most severe following 10 mg of fenoterol. Of the 35 reports, 26 were considered moderately severe, and one (global anxiety and inability to concentrate) was considered severe. Following high-dose theophylline, only six of 21 reports were considered moderately severe, and following 130 mg of theophylline with 2.5 mg or 5 mg of fenoterol, only 5 of 21 and 10 of 23 reports, respectively, were considered moderately severe; none was considered severe. All of the reported side effects following low-dose theophylline were mild.

Gastrointestinal symptoms were seen primarily following high-dose theophylline, with tremor and CNS symptoms seen more frequently when fenoterol was given. Although side effects were both more frequent and more severe with the higher dose of theophylline, the individual occurrence of side effects did not correlate with serum theophylline levels.

Treatment effects on heart rate are shown in Table 5. Resting heart rates were almost identical on the six testing days. Two hours following 10 mg of fenoterol, heart rate had increased 23 beats/min (range, -8 to 5 beats/min). These changes were significantly different from the placebo response (P < .001), as were the smaller increases seen following 130 mg of theophylline with 5 mg of fenoterol (P = .003). The changes following high-dose theophylline, 130 mg of theophylline, or 130 mg of theophylline with 2.5 mg of fenoterol were not significantly different from those following placebo. Maximal heart rates during exercise were not affected, nor were heart rates following recovery from exercise.

Table 4—Adverse Reactions Following Test Medications

<table>
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<td>Total no. of adverse reactions reported</td>
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<tr>
<td>Central nervous</td>
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<td>10</td>
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<tr>
<td>Neuromuscular</td>
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<td>Gastrointestinal</td>
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<td>3</td>
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<td>3</td>
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*Includes: subjective fatigue, garrulity, dizziness, pruritus.

Table 5—Effect of Medications on Heart Rate

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<tr>
<th></th>
<th>F₁₀</th>
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<td>10</td>
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<tr>
<td>Maximum during exercise</td>
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<td>179</td>
<td>175</td>
<td>178</td>
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<tr>
<td>5 minutes following exercise</td>
<td>115</td>
<td>109</td>
<td>98</td>
<td>107</td>
<td>111</td>
<td>100</td>
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</table>

*Mean beats/min.

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**DISCUSSION**

Both theophylline and fenoterol were demonstrated to be effective bronchodilators when taken orally. The effects of theophylline have been shown by others to be dependent on serum drug levels, and in this study bronchodilation was significantly greater at mean serum levels of 12.5 μg/ml than at levels of 6.1 μg/ml. The bronchodilation shown in this study following 10 mg of fenoterol is similarly comparable to that in previous studies with this drug\(^\text{16}\) and to studies with other orally effective β-adrenergic agonists.\(^\text{22-24}\)

The bronchodilatory effects of theophylline and fenoterol were clearly additive. The addition of a half-dose of fenoterol (5 mg) approximately doubled the pulmonary function changes seen following 130 mg of theophylline alone, so that bronchodilatation was comparable to that seen with theophylline levels twice as high. Previous studies\(^\text{1-3}\) with other adrenergic agonists and theophylline preparations have shown partially additive effects. However, the protocol used in the present experiment differed slightly from that in previous studies, in that low-dose combinations were compared with single high doses. This approach allowed not only clearer demonstration of additive effects, but it was also possible to show that when 2.5 mg of fenoterol was given with low-dose theophylline, bronchodilation increased substantially, suggesting that the effects might even be synergistic.

The effects of the two drugs as modulators of exercise-induced asthma were not as clear. If the net effects of treatment (comparing pulmonary function before medication with function after exercise) are considered, it would appear that both fenoterol and theophylline had quite marked effects on exercise-induced asthma and that the effects are additive.

However, any such conclusions overlook a major contribution of drug-induced bronchodilation that allowed subjects to begin exercise with more normal pulmonary function. Looking at exercise-induced asthma in isolation, as shown in Figure 3, it is apparent that none of the treatments actually had a marked effect on the pulmonary response to the challenge, and that the effects of combining half-doses of the two drugs are not as great as those of a full dose of either drug alone.

The disparity between the significant effects of these drugs as bronchodilators and their lesser effects on exercise-induced asthma is similar to the results of other studies with oral doses of β-adrenergic agonists. Anderson et al\(^\text{14}\) showed that comparable bronchodilatation was produced by both a 5-mg oral dose of salbutamol and a 250-μg inhaled dose, but that only the inhaled dose affected exercise-induced asthma. It was concluded that greater pulmonary concentrations are required to inhibit exercise-induced asthma than to effect bronchodilation. This conclusion is supported by other studies that show that ephedrine, a relatively weak adrenergic agonist, may produce significant bronchodilatation without affecting exercise-induced asthma.\(^\text{12,13}\)

From the point of view of the asthmatic patient, it is the net effect of these drugs that is most easily appreciated. Pulmonary function abnormalities reflect symptomatic airflow obstruction, and treatment that most effectively limits the severity of obstruction might be viewed as the most effective, regardless of the mechanism of this limitation.

All three effective regimens—high-dose theophylline, 10 mg of fenoterol, or 130 mg of theophylline with 5 mg of fenoterol—were associated with significant toxicity. Although it might be anticipated that this combination of low doses of fenoterol and theophylline would reduce the dose-dependent side effects of each, such was not the case in this trial. Specific side effects did vary. Fenoterol, for example, was associated with cardiovascular and neurologic symptoms, while theophylline more frequently produced gastrointestinal distress.

The tachycardia seen following oral fenoterol and other adrenergic agonists\(^\text{22-24}\) is of particular concern when these drugs are recommended for use before exercise, especially competitive athletics. Significant resting tachycardia suggests that there might be a greater cardiovascular risk during the exercise stress, and the significance of this risk has not yet been adequately studied. In the present study, heart rates and ECG tracings during exercise were not affected, even in the one subject whose heart rate before exercise was 124 beats/min. However, stress testing using more appropriate techniques for cardiovascular monitoring is necessary to evaluate adequately the effects. Until these effects are reported, the implication of risk remains, and oral adrenergic agonists cannot be said to be the treatment of choice.

The drugs of choice for the prevention of exercise-induced asthma are the inhaled adrenergic agonists, which are extremely effective in doses small enough to be without cardiovascular side effects.\(^\text{14}\) In addition, both cromolyn sodium\(^\text{28}\) and oral theophylline in appropriate doses\(^\text{40}\) are effective with less cardiovascular toxicity than found with oral doses of adrenergic agonists.

In summary, an orally effective adrenergic agonist and theophylline were found to have additive effects as bronchodilators, while their effects in preventing exercise-induced asthma were not significantly addi-
tive. Moreover, the frequency and severity of side effects increased with the combinations of the adrenergic agonist with theophylline, mitigating even their added value as bronchodilators.

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REFERENCES

12 Bierman CW, Pierson WE, Shapiro GG. Exercise-induced asthma: pharmacological assessment of single drugs and drug combinations. JAMA 1975; 234:295-300
13 Eggleston PA, McMahan SA. The effect of fenoterol on exercise-induced asthma. Chest (suppl) 1978; 73:1006-08
23 O'Donnell TV, Butler GM, Tocker MD. A comparison of orciprenaline and salbutamol administered orally in 12 adult asthmatic patients. Postgrad Med J 1971 (suppl); 47:115-21