Bronchodilator Effect of a New Oral Beta Adrenoreceptor Stimulant, Th1165a*

A Comparison with Metaproterenol Sulfate

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In a single-blind study the short-term effects of oral administration of Th1165a (5, 10, 15, and 20 mg), metaproterenol sulfate (Alupent) (20 mg), and placebo on ventilatory function, pulse rate, and systolic and diastolic blood pressure were compared over a period of six hours in ten patients with stable, reversible obstructive airway disease. Both Th1165a (5, 10, 15, and 20 mg) and metaproterenol administration caused significant bronchodilation of rapid onset (30 minutes), but the bronchodilator effect of Th1165a (10, 15, and 20 mg) was greater and lasted longer (six hours vs three hours) than that of metaproterenol. A dose-dependent bronchodilator effect was recognizable after administration of Th1165a. The 20-mg dose of metaproterenol sulfate and the 5-mg and 10-mg doses of Th1165a produced minimal side effects. Larger doses (15 and 20 mg of Th1165a caused significant increases in pulse rate. Mild and transient tremors were the most common side effect after administration of Th1165a.

Metaproterenol sulphate (Alupent) is chemically related to the classic sympathomimetic amine, isoproterenol. It differs from isoproterenol by having a resorcinol, instead of a catechol, nucleus, i.e., the hydroxyl group at the 4-position on the ring has been moved to the 5-position (Fig 1). As such, metaproterenol is immune to metabolic inactivation by catechol-o-methyl transferase and sulfatase enzymes. As a result, metaproterenol has a longer duration of action than isoproterenol12 and is effective after oral administration.

Terbutaline, a recently released N-tertiary resorcinol, is a bronchodilator with a relatively long duration of action and minimal side effects.5,4

A third member of the resorcinol family, the hydroxyphenyl derivative of metaproterenol, Th1165a (Berotec), has been shown to be an orally effective β-adrenoreceptor stimulator more potent than metaproterenol,5,9 with fewer cardiovascular side effects.10 Moreover, Th1165a recently has been shown to be a slightly more powerful bronchodilator than salbutamol.11-14 Th1165a has been used in Europe and other countries in the treatment of obstructive pulmonary diseases for the past ten years with good results.8,15-17

The aim of this study was to evaluate the effect of four oral doses of Th1165a (5, 10, 15, and 20 mg) and to compare it with that of metaproterenol (20 mg) and placebo on ventilatory function, pulse rate, and arterial blood pressure in patients with reversible obstructive airway diseases in a single-blind crossover trial.

Figure 1. Structural formulas of isoproterenol, metaproterenol sulfate (Alupent), and Th1165a (Berotec).
Table 1—Clinical Details of Patients Studied

<table>
<thead>
<tr>
<th>Patient, Sex</th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>Percent of Predicted FEV₁</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, F</td>
<td>44</td>
<td>157</td>
<td>65</td>
<td>52</td>
<td>Bronchial asthma</td>
</tr>
<tr>
<td>2, F</td>
<td>46</td>
<td>150</td>
<td>64</td>
<td>66</td>
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<tr>
<td>3, M</td>
<td>20</td>
<td>193</td>
<td>73</td>
<td>80</td>
<td>Bronchial asthma</td>
</tr>
<tr>
<td>4, M</td>
<td>36</td>
<td>185</td>
<td>82</td>
<td>58</td>
<td>Bronchial asthma</td>
</tr>
<tr>
<td>5, M</td>
<td>65</td>
<td>173</td>
<td>73</td>
<td>57</td>
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<tr>
<td>6, F</td>
<td>39</td>
<td>165</td>
<td>82</td>
<td>77</td>
<td>Bronchial asthma</td>
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<tr>
<td>7, M</td>
<td>34</td>
<td>178</td>
<td>88</td>
<td>47</td>
<td>Bronchial asthma</td>
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<tr>
<td>8, F</td>
<td>52</td>
<td>168</td>
<td>68</td>
<td>42</td>
<td>Asthmatic bronchitis, emphysema</td>
</tr>
<tr>
<td>9, M</td>
<td>46</td>
<td>173</td>
<td>83</td>
<td>42</td>
<td>Asthmatic bronchitis</td>
</tr>
<tr>
<td>10, M</td>
<td>41</td>
<td>175</td>
<td>71</td>
<td>58</td>
<td>Asthmatic bronchitis</td>
</tr>
<tr>
<td>Mean</td>
<td>42</td>
<td>172</td>
<td>75</td>
<td>58</td>
<td>...</td>
</tr>
<tr>
<td>Range</td>
<td>20-65</td>
<td>150-193</td>
<td>64-88</td>
<td>42-80</td>
<td>...</td>
</tr>
</tbody>
</table>

Materials and Methods

Ten ambulatory patients (four women and six men) aged 20 to 65 years (mean, 42 years) and weighing 64 to 88 kg (141 to 194 lb; mean, 75 kg [165 lb]) were studied (Table 1). All patients had suffered from asthmatic or bronchitic symptoms, including intermittent cough, wheezing, dyspnea, and sputum production for several years but had reasonably stable pulmonary function during the period of this investigation. None had histories of diabetes, heart disease, hypertension, or hyperthyroidism. One patient was a known smoker; however, he did not smoke during the study period. The patients exhibited mild to severe degrees of airway obstruction shown by decreases in the forced expiratory volume in one second (FEV₁) of 42 to 80 percent of the predicted value, with a mean value of 58 percent of predicted. The lower limit of normal in our laboratory is 85 percent of predicted. All patients had shown evidence of reversible airway obstruction indicated by an improvement of at least 20 percent of the predicted value of FEV₁, following the administration of isoproterenol aerosol. The nature of the study was explained to the patients, and all gave their consent.

The patients were requested to come to the laboratories on six test days at the same time each day. They were asked not to use any oral, rectal, injectable, or long-acting aerosol bronchodilator drug for 12 hours or any short-acting aerosol bronchodilator for four hours prior to coming to the laboratory each morning for testing. After testing for 30 minutes, the patients underwent measurements of blood pressure, pulse rate and forced spirometric studies. The spirometric studies were performed on a Stead-Wells water-sealed spirometer, and the following values were calculated from the spirogram: forced vital capacity (FVC), FEV₁, and forced midexpiratory flow (FEF 25-75%).

Two sets of control observations were obtained at 30 and 15 minutes prior to the oral administration of the test drugs. Studies were repeated at 30, 60, 90, 120, 180, 240, and 360 minutes after drug administration. The patients were required to repeat the FVC maneuver at least three times at each time interval, and the spirogram that showed the highest value for FEV₁ was used for all calculations.

Eight patients were given increasing doses of Th1165a of 5 mg, 10 mg, and 15 mg; while two patients received the drug

Table 2—Control (Pretreatment) Data on Ventilatory and Cardiovascular Functions in Ten Patients with Reversible Obstructive Airway Disease*

<table>
<thead>
<tr>
<th>Data</th>
<th>Placebo</th>
<th>5 mg</th>
<th>10 mg</th>
<th>15 mg</th>
<th>Metaproterenol Sulfate, 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>9</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>FVC, L</td>
<td>3.2 ± 0.4</td>
<td>3.0 ± 0.3</td>
<td>3.1 ± 0.4</td>
<td>3.0 ± 0.4</td>
<td>3.3 ± 0.3</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.9 ± 0.3</td>
<td>1.8 ± 0.2</td>
<td>1.8 ± 0.3</td>
<td>1.8 ± 0.3</td>
<td>1.9 ± 0.3</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>73.1 ± 3.0</td>
<td>81.0 ± 3.1</td>
<td>79.6 ± 4.4</td>
<td>76.6 ± 3.3</td>
<td>76.2 ± 2.8</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>121 ± 12</td>
<td>127 ± 9</td>
<td>118 ± 7</td>
<td>117 ± 8</td>
<td>120 ± 9</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79 ± 6</td>
<td>76 ± 6</td>
<td>75 ± 4</td>
<td>76 ± 3</td>
<td>76 ± 4</td>
</tr>
</tbody>
</table>

*Table data are means ± SE.
in the sequence of 10 mg, 15 mg, and 5 mg. Only three of the ten patients studied received the 20-mg dose. Metaproterenol sulfate (20 mg) and the placebo were given in a random fashion at some point in the course of the studies. Only the patient was unaware of the content of the test substances. One patient (patient 9) did not receive the placebo.

The patients were closely observed, and subjective side effects of nervousness, restlessness, tremors, headaches, and nausea were recorded throughout each study day.

The data on pulmonary function, pulse rate, and blood pressure at each time interval after the administration of the test drug were compared to their respective control values using the t-test for paired actual values. Changes in pulmonary function indices, pulse rate, and blood pressure with different doses of test drugs were then compared using the t-test for comparing two means. Only P values below 0.05 were considered significant.

RESULTS

The mean pretreatment values of ventilatory and cardiovascular functions in the ten patients studied are shown in Table 2. The differences in pretreatment values for FVC and FEV1 before oral administration of placebo, Th1165a, and metaproterenol were not statistically significant (P > 0.05). In Figures 2 to 4, the mean values of FVC, FEV1, and FEF25-75% over the six hours following the oral administration of the tested drugs have been plotted as the percentage of change from pretreatment values.

Administration of metaproterenol sulfate (20 mg) and of the various doses of Th1165a (5, 10, 15, and 20 mg) significantly improved all ventilatory functions (P < 0.05), whereas the placebo had no significant effect (P > 0.05). Administration of metaproterenol produced a significant increase in all ventilatory functions (P < 0.05) at each time increment from 30 to 180 minutes after oral administration, reaching maximal effect at about 90 minutes.

All ventilatory functions were significantly improved (P < 0.05) from 30 minutes to 240 minutes after the administration of 5 mg of Th1165a and from 30 minutes through 360 minutes after the larger doses (10, 15, and 20 mg), reaching maximal effect at about 120 minutes. The duration of effectiveness was more than six hours, as evidenced by the sustained increases of FEV1 and FEF25-75% (Fig 3 and 4).

The time interval between oral administration of each of the tested drugs and maximal bronchodilator response showed individual variations of 60 to 120 minutes for metaproterenol and from 90 to 180 minutes for all doses of Th1165a. Figure 5 shows the
mean peak effect on FEV₁ and FEF25-75% after administration of each of the tested agents. No significant differences could be found when results from the 5-mg dose of Th1165a and the 20-mg dose of metaproterenol sulfate were compared (P > 0.05). All of the larger doses of Th1165a produced significantly greater increases in FEV₁ and FEF25-75% when compared to either the 5-mg dose of Th1165a or the 20-mg dose of metaproterenol sulfate (P < 0.05), indicating a dose-dependent effect.

When the bronchodilator activity of Th1165a and metaproterenol is compared, it is evident that Th1165a at the 10-mg or greater dose causes greater bronchodilation and has a more prolonged action than metaproterenol sulfate at the 20-mg dose.

The maximum mean changes in pulse rate and systolic and diastolic blood pressure due to the tested drugs are shown in Table 3. A mild nonsignificant increase (P > 0.05) of less than ten beats per minute over the respective control pretreatment pulse rates was observed after oral administration of Th1165a (5-mg and 10-mg doses), metaproterenol (20 mg), and placebo; however, after a larger dose of Th1165a (15 mg), a significant increase (P < 0.05) in pulse rate occurring at one to four hours was observed, reaching a maximum of 21 beats per minute over the control pretreatment value at 90 minutes.

A dose-dependent increase in pulse rate was noted following the oral administration of Th1165a; however, the increase in pulse rate noted after the different doses of Th1165a (5 vs 10 mg, and 10 vs 15 mg) did not reach significant levels. The only significant increase in heart rate (P < 0.05) was observed...
when we compared the effect of the 5-mg dose with that of the 15-mg dose of Th1165a.

The mean changes in both systolic and diastolic blood pressure from the control levels were not significant (P > 0.05) for Th1165a, metaproterenol, and placebo. When a change was observed, it was most often a fall in diastolic pressure coincident with the peak bronchodilator effect.

Other subjective effects observed for the tested agents are shown in Table 3. The most frequent complaint after administration of the various doses of Th1165a was tremor, which was mild and variable in time of onset (30 to 120 minutes). These tremors were observed in six patients and were transient in nature, lasting from 30 to 60 minutes. Tremors were particularly noticeable with the larger doses. Only one patient had transient tremor after administration of metaproterenol.

**DISCUSSION**

Reversible obstructive airway disease is a major cause of morbidity in the United States. Reduction of airway resistance in the airway affords considerable relief to these patients and often proves decisive in averting further progression of the symptoms. Since the goal in managing the patient with chronic asthma is around-the-clock protection, the β-adrenergic stimulant agent ideally should be a reasonably long-acting and orally effective bronchodilator with few side effects. This clinical comparison of the new resorcinol compound, Th1165a, with metaproterenol documents some advantages of the new drug over metaproterenol.

This study was single-blind by request of the supplier, as the principal objective of the study was to find the dose which was effective but tolerable from the standpoint of side effects. Also, there was no desire to jeopardize the cooperation of the subjects or the success of the study by the unfortunate event of giving a patient a 20-mg dose first and observing profound side effects. Then either the patient or the investigator might wish to discontinue the study in the fear that worse side effects might be experienced with subsequent doses.

These studies show that both metaproterenol and Th1165a have a rapid onset and long-lasting bronchodilator action. The bronchodilator effect of Th1165a lasted significantly longer than that of metaproterenol (six hours vs three hours). Although the administration of higher doses of Th1165a (15 mg and 20 mg) produced greater bronchodilation (Fig 2 and 3), these doses were associated with significant increases in heart rate and a greater frequency of side effects (Table 3). Tremors were the most common side effect after administration of Th1165a but were usually transient. The optimal effective dose of Th1165a with minimal side effects was found to be 5 to 10 mg. Since the bronchodilator action lasted more than six hours, doses at six-hour to eight-hour intervals (three to four times daily) should be sufficient to sustain adequate bronchodilator action. In this context, it is interesting that our results are in agreement with and confirm previous investigations.5,8,16,19-21

In children aged two months to 12 years, oral administration of Th1165a in three to four daily doses that varied from 0.5 mg to 5.5 mg according to age resulted in successful improvement in the majority of the cases studied with no observable side effects.20,22

Th1165a has also been found to protect against bronchospasm induced by exercise,23 histamine,7 acetylcholine,24 and provocational challenges in occupational asthma.55

Th1165a has been subjected to clinical trials by a number of investigators. All stressed that therapeutically effective doses produced no observable effect on blood pressure or pulse rate.5,6,9,16,19,26 No
cardiac, hepatic, renal, or hematologic side effects were noted in 17 volunteers after long-term administration of Th1165a by aerosol after 30 days, or in 30 patients with reversible obstructive airway diseases after six months.

In summary, we found that orally administered Th1165a in a dose of 5 to 10 mg is an effective bronchodilator agent with minimal side effects. It produces a rapid onset of action, and its bronchodilator effect is of greater magnitude and more prolonged duration than that noted for metaproterenol sulfate (20 mg). Although larger doses of orally administered Th1165a cause a greater degree of bronchodilation, they are associated with further increases in pulse rate and more frequent side effects. Our study adds weight to the conclusion reached on the basis of prior clinical experience with Th1165a that this drug is an effective new oral bronchodilator for the treatment of reversible obstructive airway disease. Additional studies are required to compare the short-term and long-term effects of orally administered Th1165a with those of other new, orally effective β-adrenergic agents.

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