Comparison of the Effects of Labetalol and Hydrochlorothiazide on the Ventilatory Function of Hypertensive Patients with Asthma and Propranolol Sensitivity*

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Previous studies have shown that labetalol, a new alpha- and beta-adrenergic antagonist, is relatively safe for the treatment of hypertension in patients with chronic obstructive pulmonary disease (COPD). This multicenter study was designed to evaluate its effects in hypertensive patients with asthma and propranolol sensitivity. Hypertension was successfully controlled in 18 of 21 patients who received labetalol in increasing doses, up to 1,200 mg/day. The decrease in mean FEV, (1.5 percent) two hours after the highest dose of labetalol was not statistically significant, although there was a gradual decline in mean baseline FEV, during the four-week treatment period. Antihypertensive agents other than adrenergic antagonists should be considered for the management of hypertension in patients with asthma, especially those with marked reversibility of airflow. If treatment with beta-adrenergic antagonists is indicated, labetalol is recommended over other currently available agents.

Beta adrenergic antagonists are widely used anti-hypertensive agents with therapeutic effectiveness similar to that of methyldopa and thiazide diuretics. Their advantages over other antihypertensive medications include a lack of postural hypotension, effectiveness in the supine position, and their potential cardioprotective ability. An important consideration with currently available beta-adrenergic antagonist drugs is their ability to block the beta-adrenergic receptors in the lungs, resulting in worsened ventilatory function in patients with obstructive lung disease. Two currently available beta-adrenergic antagonist drugs, metoprolol and atenolol, have relative cardioselectivity and, at low doses, have minimal effects on bronchial smooth muscles; however, in higher doses, these drugs may increase the degree of airflow obstruction in patients with lung disease.

Labetalol hydrochloride is a new beta-adrenergic blocking agent which competitively inhibits both alpha- and beta-adrenergic receptors. This agent has been marketed in Europe since 1975 and has recently become available commercially for the treatment of hypertension in this country. Previous studies have shown that labetalol is relatively safe for use in hypertensive patients who have obstructive airways disease. The present study was designed to evaluate the effectiveness and safety of therapy with oral labetalol in a group of patients with both hypertension and asthma who had a significant increase in obstruction to air flow after a single dose of oral propranolol.

**MATERIALS AND METHODS**

**Selection of Subjects**

Patients between the ages of 18 and 70 years with mild-to-moderate essential hypertension and bronchial asthma were selected for the study. Hypertension was defined as a sitting diastolic blood pressure of 95 to 115 mm Hg on two consecutive visits while taking no antihypertensive medication. All patients had mild-to-moderate asthma, as defined by the American Thoracic Society criteria, with a history of at least one attack of acute bronchospasm requiring medication within the previous year. Patients were excluded if they had congestive heart failure, cardiac conduction block, previous cerebrovascular accident, recent myocardial infarction or significant hepatic, hematologic or renal disease. This study was approved by the institutional review committees for human studies at each hospital, and informed consent was obtained.

**Study Plan**

The study consisted of initial two-to-four week placebo washout phase, propranolol challenge, and a four-week treatment phase (Fig 1). During the two-to-four week placebo washout phase, patients were treated with a placebo tablet twice daily and were examined at weekly intervals. All antihypertensive and bronchodilator drug therapy was discontinued except for oral or inhaled corticosteroid and oral theophylline therapy, which was continued at stable maintenance levels, provided the patient had been on long-term therapy with these agents. In addition, metered dose inhalers containing albuterol were given to each subject for use only in the event of an acute asthma attack. The canisters were weighed at each weekly evaluation to determine usage during the previous week. All bronchodilator therapy was discontinued for at least six hours prior to pulmonary function tests.

Patients who did not maintain a sitting diastolic blood pressure...
between 95 and 115 mm Hg on at least two consecutive weekly visits were dropped from the study. All patients who successfully completed the washout phase underwent an oral propranolol challenge. They were first given 40 mg of propranolol and, if their FEV₁ failed to decrease by 20 percent or more, they were given 80 mg of propranolol on a separate study day. If once again their FEV₁ did not decrease by at least 20 percent, they were dropped from the study.

Subjects who responded to treatment with propranolol entered the four-week treatment phase, during which they received labetalol or hydrochlorothiazide and continued to be evaluated weekly. Labetalol was titrated at each visit, from 100 up to 600 mg twice daily, the end point being a drop in diastolic blood pressure below 90 mm Hg and at least 10 mm Hg from baseline. Hydrochlorothiazide was titrated from 25 to 50 mg twice daily until the same end point was reached. Patients received diary cards on which they recorded any adverse symptoms or experiences between evaluation periods.

At each weekly visit, subjects were asked about adverse reactions and diary cards were collected. Baseline heart rate, blood pressure and spirometric measurements were repeated and the appropriate dose of medication, based on diastolic blood pressure level, was then administered. Spirographic studies were performed, and blood pressure and heart rate were determined two hours after ingestion of the medication.

**Statistical Analysis**

The two treatments (with labetalol and hydrochlorothiazide) were compared using analysis of variance. The immediate effects of administration of both drugs on ventilatory function were evaluated by comparing FEV₁ level two hours after the largest dose of antihypertensive medication given on the last treatment day to baseline FEV₁ prior to drug administration on the same day. Long-term effects were evaluated by comparing FEV₁ before treatment on each evaluation day during phase two with the mean of the last two pre-treatment FEV₁ levels during the placebo washout period. Antihypertensive effects of the drugs were evaluated by comparing the sitting diastolic blood pressure prior to drug administration on each treatment day with the mean of the last two sitting diastolic blood pressures during the placebo washout period.

**RESULTS**

**Patient Characteristics**

Of the 41 patients who entered the treatment phase of the study, 21 received therapy with labetalol and 20 received hydrochlorothiazide treatment (Table 1). The ratio of men to women was similar in both groups. Mean age was 54 years in the labetalol group and 59 years in the hydrochlorothiazide group. The preponderance of middle-aged males reflects the fact that two of the participating hospitals were Veterans Administration hospitals. Three of the 21 patients in the labetalol group and five of the 20 in the hydrochlorothiazide group were black. There were no significant differences in mean baseline systolic blood pressure, diastolic blood pressure, FEV₁, or FEV/FVC levels between the two treatment groups.

**Propranolol Challenge**

The responses of the 41 patients to oral propranolol challenge are shown in Table 2. In the labetalol group, mean FEV₁ decreased from 1,707 ml to 1,180 ml two hours after receiving propranolol, a decrease of 32 percent. A similar decrease was seen, from a mean value of 1,823 ml to 1,250 ml, in the patients receiving hydrochlorothiazide, a decrease of 31 percent. The fall in FEV₁ after administration of propranolol was significant in both groups.

**Control of Hypertension**

Of the 21 patients who received therapy with labetalol, 18 completed the four-week treatment phase; the remaining three were dropped due to lack of blood pressure control. Of the 20 patients who received therapy with hydrochlorothiazide, 18 completed the treatment phase; the other two were dropped due to lack of blood pressure control. Average maximum daily dose of labetalol in the 18 patients who completed the study was 557 mg, while the average maximum daily dose of hydrochlorothiazide was 72 mg.

**Table 1—Population Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Labetalol group</th>
<th>Hydrochlorothiazide group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Male/female</td>
<td>16/5</td>
<td>15/5</td>
</tr>
<tr>
<td>Mean age (Yrs)</td>
<td>54</td>
<td>59</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>146 ± 3*</td>
<td>155 ± 4*</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>100 ± 1*</td>
<td>102 ± 1*</td>
</tr>
<tr>
<td>Baseline FEV₁, (ml)</td>
<td>1,688 ± 128*</td>
<td>1,763 ± 176*</td>
</tr>
<tr>
<td>Baseline FEV₁/FVC</td>
<td>0.58 ± 0.03*</td>
<td>0.58 ± 0.03*</td>
</tr>
</tbody>
</table>

*Mean ± SEM
Table 2—Changes in FEV₁ (ml) After Oral Propranolol

<table>
<thead>
<tr>
<th></th>
<th>Labelol group</th>
<th>Hydrochlorothiazide group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before propranolol</td>
<td>1,707 ± 133*</td>
<td>1,823 ± 181*</td>
</tr>
<tr>
<td>2 hrs. after propranolol</td>
<td>1,180 ± 125*</td>
<td>1,250 ± 132*</td>
</tr>
<tr>
<td>% decrease</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>P†</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Mean ± SEM
†Significance of change from before to 2 hours after propranolol.

Ventilatory Function

Short-term effects of therapy with labelol and hydrochlorothiazide were evaluated by comparing FEV₁ levels before and two hours after administration of the maximum antihypertensitve drug dose on the last treatment visit. The results of this comparison are shown in Table 3. Pretreatment FEV₁ on the last treatment day was 1,578 ml in the labelol group, a value significantly lower than the mean pretreatment value of 1,905 ml in the hydrochlorothiazide group. Two hours after administration of the highest dose of labelol, mean FEV₁, was 1,554 ml, a decrease of 1.5 percent; in the hydrochlorothiazide group, mean FEV₁ decreased only 1 ml (0.05 percent). Mean change in FEV₁, two hours after maximum dose was not significant in either group.

Long-term effects of the two antihypertensive agents are shown in Table 4. Initial mean FEV₁ was lower in the labelol group (1,662 ml vs 1,760 ml), and there was a gradual drop in mean baseline FEV₁ in the labelol group, reaching a maximum of 156 ml after three weeks of therapy. There was an increase in mean baseline FEV₁ in patients receiving hydrochlorothiazide, reaching a maximum of 145 ml at the last treatment visit. Although there was a decline in mean baseline FEV₁ with increasing doses in the labelol group, the change was not significant in either group.

Other Side Effects

Neither antihypertensive agent was discontinued because of the presence of significant side effects. One patient who received hydrochlorothiazide complained of dryness of the mouth, and one patient in the labelol group had leg cramps. One patient in each group noted increased fatigue.

Table 3—FEV₁ (ml) Before and Two Hours After Highest Dose of Antihypertensive Agent

<table>
<thead>
<tr>
<th></th>
<th>Labelol (n = 19)</th>
<th>Hydrochlorothiazide (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before highest dose</td>
<td>1,578 ± 135*</td>
<td>1,905 ± 256*</td>
</tr>
<tr>
<td>After highest dose</td>
<td>1,554 ± 137*</td>
<td>1,904 ± 242*</td>
</tr>
<tr>
<td>Change (%)</td>
<td>−1.5</td>
<td>−0.05</td>
</tr>
<tr>
<td>P§</td>
<td>&gt;0.5</td>
<td>&gt;0.5</td>
</tr>
</tbody>
</table>

*Mean ± SEM
§Significance of change from before to 2 hours after propranolol.

Table 4—Effects of Hydrochlorothiazide and Labetalol on FEV₁ During Four-Week Treatment Period

<table>
<thead>
<tr>
<th></th>
<th>No. of subjects</th>
<th>Hydrochlorothiazide FEV₁ (ml)</th>
<th>No. of subjects</th>
<th>Labetalol FEV₁ (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>20</td>
<td>1,760 ± 170*</td>
<td>21</td>
<td>1,682 ± 118*</td>
</tr>
<tr>
<td>Visit 1</td>
<td>20</td>
<td>1,802 ± 184*</td>
<td>21</td>
<td>1,665 ± 116*</td>
</tr>
<tr>
<td>Visit 2</td>
<td>20</td>
<td>1,782 ± 203*</td>
<td>19</td>
<td>1,654 ± 121*</td>
</tr>
<tr>
<td>Visit 3</td>
<td>19</td>
<td>1,624 ± 225*</td>
<td>19</td>
<td>1,526 ± 137*</td>
</tr>
<tr>
<td>Visit 4</td>
<td>18</td>
<td>1,906 ± 256*</td>
<td>19</td>
<td>1,578 ± 135*</td>
</tr>
<tr>
<td>Maximum change</td>
<td></td>
<td>+145</td>
<td></td>
<td>−156</td>
</tr>
</tbody>
</table>

*Mean ± SEM

Discussion

The decision to include a propranolol challenge as a part of the protocol was made after considerable debate. A drop in FEV₁, following oral administration of propranolol was added to the criteria for patient entry in order to increase the significance of the results. Exercise was used previously by the authors as a nonspecific challenge and was found to be unreliable in older patients. At the beginning of the study, all candidates were challenged with 80 mg of oral propranolol; however, one patient at each of the three study centers developed severe bronchospasm requiring therapy with bronchodilators and lasting up to three days. Following this event, the protocol was amended so that patients first received a 40 mg dose of propranolol, and if the FEV₁ did not decrease by 20 percent or more, the larger dose was given on a separate day.

The results of this study indicate that a majority of patients with mild-to-moderate hypertension can be controlled successfully with oral labelol twice daily. These results are consistent with previous reports that labelol is an effective antihypertensive agent. While no previous studies have reported the chronic effects of therapy with labelol on ventilatory function in asthmatic subjects, the acute effects have been evaluated in both normal and asthmatic subjects. In six healthy volunteers, Maconochie et al found that administration of 400 mg of oral labelol did not enhance the fall in FEV₁ after a histamine challenge. They hypothesized that the alpha-adrenergic receptor blocking activity of labelol should make it less likely to cause bronchoconstriction in asthmatic subjects. Skinner et al found that mean FEV₁ decreased only 20 ml 15 min after the intravenous administration of 20 mg of labelol to ten asthmatic subjects.

While the effects of a single dose of labelol on airflow are minimal, there was a trend toward decrease in FEV₁ over the four-week period of this trial. This trend may be important in that the dosage was titrated upward at each of the four visits until blood pressure was satisfactorily controlled; thus, the average daily dose was highest at the last visit. This suggests that there may be a decrease in ventilatory function in some
propranolol-sensitive asthmatic subjects when higher doses of labetalol are administered, as has been reported with the cardioselective beta-adrenergic blocking drugs, metoprolol and atenolol.12,24 In spite of the gradual drop in FEV1, patients did not require more bronchodilator medication and did not report an increase in dyspnea or wheezing. Long-term deterioration of lung function following labetalol administration was not seen in patients with hypertension and chronic obstructive pulmonary disease in one study, although in a separate study using the same protocol, there was a gradual deterioration in ventilatory function with labetalol therapy.25

Because of the availability of other effective anti-hypertensive agents, beta-adrenergic antagonist drugs are not recommended for the initial treatment of hypertension in asthmatic subjects, especially those with marked airway responsiveness. Alternative agents which might be considered in these patients include diuretics, alpha-adrenergic antagonist drugs and calcium channel-blocking agents. Although the calcium inhibitor drugs have not been approved for use as antihypertensive agents, they are frequently used for this purpose with good results.24 These agents have been shown to protect against nonspecific bronchial challenges26-27 and, in a recent report, verapamil compared favorably with labetalol for the treatment of hypertension in a group of patients with obstructive airways disease.28

If a decision is made to use a beta-adrenergic antagonist drug because of failure to obtain a satisfactory response with alternative agents or because of patient intolerance, then labetalol is recommended over other currently available agents because of its effectiveness and relative safety. Because of the trend toward a decrease in FEV1 with increasing doses of labetalol, patients with asthma should be observed closely with spirometric examinations or peak flow determinations for the first few weeks, while the dose is being adjusted for blood pressure control.

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REFERENCES


