Effect of Beclomethasone Dipropionate on the Bronchial Responsiveness to Propranolol in Asthmatics*

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The effect of four weeks of treatment with beclomethasone dipropionate (BDP, 500 µg twice daily) on the bronchial responsiveness to propranolol was examined in 16 patients with mild asthma in a placebo-controlled, double-blind crossover study. Propranolol was inhaled in doubling concentrations and the results were expressed as the cumulative dose producing a 20 percent fall in FEV₁ (PC₂₀). After four weeks of treatment with BDP, the mean FEV₁ increased from 82.0 percent predicted to 88.1 percent predicted. The difference was significant (p<0.001). Treatment with BDP did not significantly change the responsiveness to propranolol, the geometric mean PC₂₀ being 3.17 mg/ml before and 3.64 mg/ml after BDP treatment. The recovery of FEV₁, was faster after 60 minutes of BDP treatment in comparison with placebo treatment (beyond 90 minutes). This study suggests that BDP treatment is unable to reduce bronchial responsiveness to propranolol but can accelerate the recovery of bronchoconstriction induced by propranolol in asthmatic patients.

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**BDF = beclomethasone dipropionate**

Non-specific bronchial hyperresponsiveness, a hallmark of asthma, is currently measured by standardized inhalation tests with histamine or methacholine.1,2 Bronchoconstriction induced by propranolol is considered by some workers to be a feature of bronchial hyperresponsiveness3,4 and its observation is thought to be more specific than histamine in detection of patients with asthma.4

Inhaled corticosteroids diminish bronchial responsiveness to histamine and methacholine,5-7 but there is little information as to whether these drugs can equally reduce bronchial responsiveness to propranolol. Corticosteroids are known to increase β-adrenergic receptor site concentration8,9 and to inhibit the mediator release from mast cells facilitated by propranolol.10,11

Therefore, in this study the effect of treatment with inhaled beclomethasone dipropionate (BDP) on the bronchial responsiveness to propranolol was investigated in asthmatic patients. In addition the time course of change in FEV₁ after propranolol inhalation was determined.

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**Methods**

Sixteen patients (12 male and four female) with mild asthma (mean age, 38 years; range, 20 to 48 years) gave their informed consent to participate in the study. The initial FEV₁, measured during the selection period, was not below 70 percent of predicted. All patients had an increased bronchial responsiveness to propranolol defined by a propranolol PC₂₀ (concentration causing a 20 percent fall in FEV₁) below 8 mg/ml. All patients had demonstrated a good inhaler technique and none was taking oral corticosteroids, theophyllines, cromolyn sodium (sodium cromoglycate), or anticholinergic drugs. All were maintained on a regular regimen of albuterol (salbutamol).

Patients received either two puffs (500 µg) of BDP or identical placebo twice daily for four weeks with a washout period of two weeks between treatments. Treatments were given double blind and in random order. Bronchial response was assessed by measuring FEV₁, with a spirometer (Compuspir Cosmed, Milan, Italy). Propranolol inhalation challenge was carried out at the same time of day (8 AM) before and on the 28th day of each treatment period, after albuterol therapy was withheld at least for 12 hours. After having baseline spirometry, the patients inhaled a control solution of saline 9 g/L, followed at three-minute intervals by doubling concentrations of propranolol starting at 1 mg/ml and going up to a maximum of 8 mg/ml. Aerosols were generated from a nebulizer calibrated to deliver an output of 0.150 to 0.155 ml at a flow rate of 8 L/min and inhaled by a tidal breathing for two minutes. The FEV₁ was measured 60 s after each inhalation. Inhalations were discontinued when FEV₁, had fallen by 20 percent from baseline value.
Table 1—Effect of Four-Week Treatment with Beclomethasone Dipropionate (BDP) and Placebo on Baseline Respiratory Function and Response to Propranolol

<table>
<thead>
<tr>
<th></th>
<th>FEV₁ (% Pred)</th>
<th>PC₂₀ (mg/ml)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Treatment</td>
<td>After 4 weeks</td>
</tr>
<tr>
<td>Placebo</td>
<td>82.5</td>
<td>82.8</td>
</tr>
<tr>
<td>BDP</td>
<td>82.0</td>
<td>88.1†</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>&lt;0.001</td>
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</tbody>
</table>

*Geometric mean. PC₂₀ = provocative dose causing a 20 percent fall in FEV₁. †Statistical significance with the pretreatment values p<0.01.

RESULTS

Mean values for FEV₁ as percent predicted and PC₂₀ before and after placebo and BDP treatments are shown in Table 1. There was no significant difference in the mean pretreatment baseline values for both FEV₁ and PC₂₀. Treatment with BDP caused a significant increase in mean FEV₁ (p<0.001). Treatment with placebo did not significantly change the FEV₁. The difference between mean values for FEV₁ after placebo and BDP treatments was significant (p<0.001). Immediately prior to the treatment with BDP, the mean PC₂₀ was 3.17 mg/ml; with the addition of BDP, the mean PC₂₀ increased to 3.64 mg/ml, but the difference was not significant. Treatment with placebo did not cause an increase in PC₂₀ values, the mean PC₂₀ being 3.12 mg/ml at the beginning of placebo treatment and 3.15 mg/ml at the end (Table 1).

At the end of placebo treatment, FEV₁ after propranolol challenge did not return to within 5 percent of baseline values 90 minutes after challenge. Recovery was faster after BDP treatment, with FEV₁ returning to within 5 percent of baseline 60 minutes after propranolol challenge (Fig 1).

DISCUSSION

In this study, treatment with BDP did not significantly change the airway response to propranolol, but influenced the time course of bronchoconstriction after propranolol accelerating the recovery of FEV₁. The explanation of this pattern is not easy. The exact mechanism by which propranolol induces bronchoconstriction in asthmatic patients is not completely understood. It has been suggested that the bronchoconstriction induced by propranolol might be related to increased parasympathetic tone that would exert its effect unopposed after β-blockade. This hypothesis is supported by the observation that in asthmatic patients prior administration of atropine can substantially reduce the bronchial response to propranolol. There is, however, no convincing evidence that the adrenergic system could be considered as a counter-regulating mechanism causing bronchodilatation and attenuating bronchial hyperresponsiveness.

The mediator release from mast cells may play a part in the bronchial constriction induced by propranolol. Mast cells in human lung possess β-receptors. In vitro β-agonists inhibit mediator release, including histamine and prostaglandins, and this action is antagonized by propranolol. In vivo there is some evidence that plasma adrenaline may regulate mediator release from mast cells in asthmatic patients. Propranolol may increase response to histamine and prolong the recovery from bronchoconstriction induced by histamine.

Therefore, a possible explanation is that the initial bronchoconstriction depends on the direct effect of propranolol on the β-adrenergic receptors in the bronchial smooth muscle affecting tone, while the recovery might depend on the amount of mediator release from mast cells. Alternatively, BDP might reduce the mediator release but not the response to released mediators.

In any case, the present data suggest further investigations on the effect of BDP on the β-adrenergic function in humans with asthma.

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