The Endocrinometabolic Effects of Beclomethasone Dipropionate in Asthmatic Patients*

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The endocrinometabolic effects of the aerosol administration of beclomethasone dipropionate (100 μg four times daily) were evaluated in 20 asthmatic patients (11 corticodependent and nine noncorticodependent) during one month. In the noncorticodependent group, aerosol administration of beclomethasone had no statistically significant effect on the results of the glucose tolerance test and the plasma levels of insulin; there was a slight decrease in basal levels of cortisol, but the response of the cortisol level to administration of ACTH remained quite normal. In corticodependent patients, after substitution of aerosol therapy with beclomethasone for the oral therapy with steroids, the depression of adrenal function disappeared, usually quickly (in less than one month), whereas the abnormalities in the results of the glucose tolerance test persisted. Thus, at the dosage used, beclomethasone dipropionate might have minor systemic endocrinometabolic effects.

Numerous double-blind crossover studies1-3 have demonstrated the usefulness of aerosol administration of steroids in the treatment of chronic bronchial asthma. The success of this therapy is due to the reduction of side effects, compared to oral therapy with corticosteroids; however, the frequency and the clinical relevance of the side effects obviously depend on the nature and the dosage of the drug itself. For instance, aerosol administration of beclomethasone dipropionate is reputed to give minimal adrenal suppression at a current dosage of 400 μg/day, which is able to control asthma.1,3 Whereas the effects on the hypothalamic-pituitary-adrenocortical axis have been extensively investigated,4,5 we could not find any systematic study describing the effects on the metabolism of glucose. Therefore, the present work was designed to test both metabolic and endocrine effects of therapy with beclomethasone dipropionate given to 20 asthmatic patients for a period of one month.

Materials and Methods

The effects on glucose tolerance and on the hypothalamic-pituitary-adrenocortical axis of the administration of 100 μg of beclomethasone dipropionate four times daily (by metered-dose aerosol) during one month were tested in 20 patients with bronchial asthma (defined according to the criteria of the Ciba guest symposium1). Nine patients had received no treatment with corticosteroids or ACTH for at least six months and were considered noncorticodependent. Eleven patients had been treated with prednisolone (5 to 15 mg daily) for several months and were referred to as corticodependent. In this latter group, therapy with prednisolone was replaced by oral administration of betamethasone (1.5 mg daily) at least 48 hours before the investigation started.

In each patient, tests of pulmonary function were performed, including spirometric measurements of the vital capacity (VC) and of the forced expiratory volume in one second (FEV₁) and determination of the total lung capacity (TLC) by a prolonged helium-dilution method. The airway resistance (Raw) and the thoracic gas volume (TGV) were measured in a constant-volume body plethysmograph; from these data, specific airway resistance was calculated (SRaw = Raw × TGV). The details of the methods used have been previously described.8

An oral glucose tolerance test (50 gm) was performed after an overnight fast; the plasma level of glucose was estimated with a photoelectric analyzer (Technicon Autoanalyzer) according to a technique derived from Hoffman,9 and the plasma level of insulin was determined by radioimmunoassay.10

On a consecutive day, an intravenously administered stim-
ulation test with 250μg of cosyntropin (tetracosactrin; β<sup>24</sup>-ACTH) was performed after an overnight fast; the plasma level of cortisol was measured by a highly specific radioimmunoassay using a rabbit’s antibody raised against 3-CMO-BSA-cortisol* (Raoul Leclercq, M.D., and V. Leclercq-Meyer, M.Sc., unpublished data). All tests began between 8 and 9 A.M.

The same tests were repeated in each subject after four weeks of aerosol treatment with beclomethasone dipropionate (100μg 4 times daily). In the corticodependent group, oral therapy with betamethasone was abruptly stopped when aerosol therapy was initiated. Tests of pulmonary function were not repeated in four of the 11 corticodependent patients. As far as possible, there was no change in the nature and dosage of the other drugs (generally aminophylline and β<sub>1</sub>-sympathomimetic drugs) during the experiment.

**RESULTS**

The results of the tests of pulmonary function are presented in Table 1 (means ± SD). For the seven corticodependent patients who were studied twice (Table 1), the withdrawal of oral therapy with steroids resulted in a slight deterioration of pulmonary function; however, the change was not significant (paired t-test). For the noncorticodependent patients (Table 1), pulmonary function was slightly improved after one month, with a significant decrease in Raw and SRaw. Each group was characterized by an obstructive pattern, with a decrease in FEV<sub>1</sub> and an increase in Raw more important in the corticodependent group.

The glycemic curve (Fig 1) was not significantly (analysis of variance) altered by the administration of aerosol therapy either in the corticodependent group (F = 0.01; not significant) or in the noncorticodependent group (F = 0.02; not significant). No significant difference (t-test on the means) could be found between both groups, except before the treatment with beclomethasone (at 60 minutes), when levels of glucose were slightly higher in the corticodependent group than in the noncorticodependent group (t = 2.41; P < 0.05). The difference after substitution of aerosol therapy was not more significant. An analysis of the individual curves was also performed. According to the criteria of Fajans and Conn,<sup>11</sup> three of the 11 corticodependent patients and one of the nine noncorticodependent patients had chemical diabetes before the administration of the aerosol. After one month of treatment, there was no change in the noncorticodependent group, and four of the 11 patients of the corticodependent group had some degree of glucose intolerance.

![Figure 1. Plasma levels of glucose (means ± SE) after oral absorption of 50 gm of glucose, determined before (open circles) and after (solid circles) administration of beclomethasone dipropionate in two groups of asthmatic patients.](image-url)

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*3 carboxymethyloxime cortisol coupled to BSA<sub>21</sub> bovine serum albumin.

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**Table 1—Tests of Pulmonary Function in Two Groups of Asthmatic Patients before and after Aerosol Therapy with Beclomethasone**

<table>
<thead>
<tr>
<th>Test</th>
<th>Corticodependent Group</th>
<th>Noncorticodependent Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Therapy</td>
<td>After 4 Weeks</td>
</tr>
<tr>
<td>VC, L</td>
<td>2.79 ± 1.04</td>
<td>2.39 ± 0.68</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, L</td>
<td>1.12 ± 0.64</td>
<td>0.92 ± 0.46</td>
</tr>
<tr>
<td>TLC, L</td>
<td>6.76 ± 1.39</td>
<td>6.71 ± 1.60</td>
</tr>
<tr>
<td>Raw, cm H&lt;sub&gt;2&lt;/sub&gt;O/ L/sec</td>
<td>5.45 ± 3.38</td>
<td>5.51 ± 2.25</td>
</tr>
<tr>
<td>TGV,</td>
<td>5.73 ± 1.71</td>
<td>5.87 ± 1.22</td>
</tr>
<tr>
<td>SRaw, cm H&lt;sub&gt;2&lt;/sub&gt;O/sec</td>
<td>35.00 ± 30.50</td>
<td>32.70 ± 14.70</td>
</tr>
</tbody>
</table>

* *Aerosol therapy (4 weeks in duration) with beclomethasone dipropionate was substituted for oral therapy with steroids. **NS, Not significant.
levels of cortisol in the plasma (from 10.7 ± 1.2 µg/100 ml to 8.1 ± 1.2 µg/100 ml). After the four weeks of treatment, there were no more significant differences in basal levels of cortisol in the plasma between the two groups (t = 1.32; F > 0.10).

Before the administration of aerosol therapy, the response of the cortisol level to administration of cosyntropin was significantly lower (t-test on the mean, t = 2.79; P < 0.05) in the corticodependent group than in the noncorticodependent group; the maximal changes in the levels of cortisol were 6.1 ± 1.3 µg/100 ml for the noncorticodependent group and 10.7 ± 0.9 µg/100 ml in the corticodependent

Plasma levels of insulin (Fig 2) were not altered by aerosol administration of beclomethasone either in the noncorticodependent group (F = 0.93; not significant) or in the corticodependent group (F = 2.97; not significant), and no difference existed between groups.

The results of the stimulation tests with cosyntropin are shown in Figure 3. Before the administration of aerosol therapy, basal levels (0 minutes) of cortisol in the plasma were markedly lower in the corticodependent group (2.9 ± 0.8 µg/100 ml; mean ± SE) than in the noncorticodependent group (10.7 ± 1.2 µg/100 ml; t = 5.69; P < 0.001). In the corticodependent group the replacement of oral therapy with steroids by aerosol therapy with beclomethasone resulted in a significant increase (paired t-test, t = 3.95; P < 0.005) in basal levels of cortisol in the plasma (from 2.9 ± 0.8 µg/100 ml to 6.2 ± 0.9 µg/100 ml). In contrast in the noncorticodependent group, administration of beclomethasone aerosol was followed by a slight but significant decrease (paired t-test, t = 2.42; P < 0.05) of basal
group. In the noncorticodependent group the amplitude of the response of the cortisol level was not altered by aerosol treatment (analysis of variance, F = 1.71; not significant), whereas in the corticodependent group the substitution of aerosol therapy for oral therapy with steroids was followed by a marked increase of the amplitude of the response of the cortisol level (F = 35.55; P < 0.001). The amplitude became greater than 7 μg/100 ml in all but one patient. Thus, under treatment with beclomethasone, the response of the cortisol level became similar in both groups (12.1 ± 1.1 μg/100 ml and 12.6 ± 2.1 μg/100 ml at 30 minutes).

**Discussion**

The aim of the present work was mainly to evaluate the systemic effects of administration of beclomethasone dipropionate as a metered-dose aerosol in asthmatic patients. Nevertheless, during the trial, most of the patients felt subjective improvement, and this could be confirmed by tests of pulmonary function in the noncorticodependent group. No clinical side effects were evidenced during the month of therapy, either in the noncorticodependent group or in the corticodependent group. In the latter group, pulmonary function did not significantly deteriorate after the abrupt substitution of aerosol therapy with beclomethasone for oral therapy with steroids; however, this transfer must be done cautiously, since a few cases of adrenal failure have been described in such situations.13-14 Progressive withdrawal of oral therapy with steroids is thus favored by most investigators,8,15 particularly if patients have received high oral doses of steroids. Such abrupt disruption of oral therapy could be applied in the present study because most of the corticodependent patients were hospitalized for a long term in a rehabilitation clinic and were thus under careful medical control. This procedure allowed a more precise evaluation of the characteristics of adrenal recovery than the progressive withdrawal of oral therapy with steroids.

To our knowledge, the effects of aerosol therapy with beclomethasone on the glucose tolerance test and the plasma levels of insulin have never been systematically studied. In the present work, there was no statistically significant modification in the levels of glucose or insulin after therapy with beclomethasone. The analysis of the individual curves of the corticodependent patients indicates an amelioration in one patient but also a deterioration in two others, so that in certain patients, administration of beclomethasone dipropionate might have some systemic effects on the metabolism of glucose. Those patients had no adrenal suppression.

With aerosol therapy with steroids, other authors have noted the absence of modification of the basal levels of glucose in the plasma9,14 and the good tolerance of the diabetic patient to this kind of therapy.16,17 The effects of aerosol therapy with beclomethasone on the hypothalamic-pituitary-adrenocortical axis have been more extensively studied. In healthy volunteers, oral therapy with beclomethasone dipropionate at a dosage of 4 mg/day or more reduced basal levels of cortisol.8 Inhalation of 400 μg daily did not interfere with the diurnal variations in the level of cortisol8 and did not alter significantly the basal level of cortisol after two weeks of treatment,8 although these levels were somewhat lower during the treatment than during the control period. In noncorticodependent patients, levels of cortisol remained within normal limits after two years of treatment,18 and stimulation tests with cosyntropin (Synacthen) were constantly positive18,19 except when doses of 1 mg or higher were given, which induced adrenal suppression.20-22 In the present work, after one month of treatment, a slight lowering of the basal level of cortisol and a quite normal stimulation test with cosyntropin were found. In the corticodependent patients the progressive transfer to aerosol therapy resulted in normalization of adrenal function after two to five weeks,23-25 except in rare cases.26 The same conclusions were reached by numerous other investigations using stimulation tests with cosyntropin.14,27-29 The present results agree with those conclusions, since a normal adrenal reserve was observed after one month of aerosol therapy.

Theoretically, such an adrenal response does not exclude some persistent depression of the whole hypothalamic-pituitary-adrenocortical axis; however, Kehlet and Binder20 have demonstrated the reliability of the rapid stimulation test with cosyntropin in predicting the response of the hypothalamic-pituitary-adrenocortical axis to major surgical stress in glucocorticoid-treated patients. Moreover, Spitz et al21 have found a very good correlation between the results of that test and the response to insulin-induced hypoglycemia.

The mechanism by which the aerosol administration of steroids could interfere with the metabolism of glucose and with the hypothalamic-pituitary-adrenocortical axis seems to be mainly the digestive absorption of the large portion of the aerosol which is deposited in the mouth and pharynx and swallowed. The advantage of therapy with beclomethasone dipropionate over other steroids seems to be that after digestive absorption, the drug is converted into pharmacologically inactive metabolites.
during its passage through the liver.\textsuperscript{32} This explains the paucity of endocrinometabolic effects of this drug and, as a consequence, the reduction in side effects which occur with this kind of therapy. When higher dosages were given, a resorption of the drug through the lung could be of significance,\textsuperscript{33} with the risk of increasing side effects.

REFERENCES