Nocturnal Cortisol Secretion in Asthmatic Patients After Inhalation of Fluticasone Propionate*

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Objectives: This study was designed to assess the relationship between the degree of airflow obstruction and the suppression of the hypothalamic-pituitary-adrenal axis after inhalation of fluticasone propionate (FP) in asthmatic patients with varying degrees of airway obstruction.

Study design: The nocturnal cortisol production (from 10:00 PM to 6:00 AM), defined as the integrated area under the curve of nocturnal plasma cortisol, was measured following inhalation of a placebo or a single dose of 500 μg FP at 8:00 PM in 28 patients with mild to moderate asthma, in a single, blind, 2-night study.

Results: The mean morning rise of cortisol decreased significantly following a single dose of inhaled FP. When the total nocturnal cortisol production after the second night (when the FP was inhaled) was compared to that after the first night (when the placebo was administered), it was found to have decreased by 29.4%. There was a statistically significant correlation between the FEV₁ and the fall in cortisol production just before the inhalation of FP (p < 0.001). There was no correlation between baseline cortisol production and the fall in cortisol production.

Conclusions: Our findings suggest that the degree of airway obstruction affects the systemic bioavailability of FP. FP is likely to induce a more severe decrease in nocturnal cortisol secretion in less obstructed patients. In order to reduce the risk for systemic side effects, the patient's degree of airway obstruction should be considered when planning inhaled FP treatment.

Key words: airway obstruction; asthma; inhaled glucocorticoids

Abbreviations: AUC8h = the integrated area under the curve of nocturnal plasma cortisol; FP = fluticasone propionate; HPAA = hypothalamic-pituitary-adrenal axis; IGC = inhaled glucocorticoids

Inhaled glucocorticoids (IGC) are highly efficacious in the treatment of asthma,¹ but some questions about this treatment modality remain unanswered, such as the potential for growth suppression in children and the potential for adrenal suppression and osteoporosis in both children and adults.

Certain data suggest a possible dose-response relationship with regard to IGC therapy.²⁻⁵ These studies have shown that dose-dependent suppression of the hypothalamic-pituitary-adrenal axis (HPAA) occurs in healthy volunteers and in asthmatic patients even following a single-dose inhalation of IGC.

Systemic bioavailability of IGC is mainly determined by absorption of the drug across the lung vascular bed.⁶⁻⁷ Consequently, lung deposition and systemic bioavailability might be altered by the narrowed airway caliber in patients with asthma. Peripheral lung deposition has been found to be significantly higher in normal subjects than in asthmatics inhaling salmeterol.⁸ We hypothesized that the degree of HPAA suppression in asthmatic patients is inversely related to the degree of airflow obstruction following the inhalation of corticosteroids.

Materials and Methods

Patients

Twenty-eight patients with mild to moderate asthma were studied. The patients satisfied the American Thoracic Society definition of asthma, with symptoms of episodic wheezing, cough, and shortness of breath responding to bronchodilators, and reversible airflow obstruction documented in at least one previous pulmonary function study.⁹ Patients who received oral or inhaled corticosteroids in the last 3 months were excluded from...
the study. All patients were on rescue treatment with $\beta_2$-agonists only. The patients were not allowed to use $\beta_2$-agonists 12 h before entering the study and during the study. The characteristics of the patients are summarized in Table 1. The study was approved by the institutional committee on human research, and informed consent was obtained from all patients.

Study Design

This study was designed as a single, blind, 2-night study in which, during the first night, the baseline integrated area under the curve (AUC8h) of nocturnal plasma cortisol was measured following the administration of the placebo using an inhaler (Diskhaler; Glaxo Wellcome Group; Uxbridge, Middlesex, UK), and during the second night, AUC8h was measured following inhalation of a single dose of 500 $\mu$g of fluticasone propionate (FP) by way of an inhaler (Diskhaler; Glaxo Wellcome Group). The patients were instructed to hold the inhaler away from their mouths, to exhale as far as they could, to inhale through the mouthpiece steadily and as deep as they could, and to hold their breath as long as possible. On each night, pulmonary function tests were performed following insertion of an indwelling cannula into a forearm vein in order to ensure venous access during the night without disturbing sleep. A single evening dose of an inhaled placebo (day 1) or FP (day 2) was administered at 8:00 PM, and blood samples for cortisol were taken every hour from 10:00 PM to 6:00 AM.

The FP and the placebo were administered using a standard inhaler with 500 $\mu$g per inhalation. Before enrollment, all participants were instructed carefully on the use of the inhaler.

Tests

Spirometry: The FVC and the FEV1 were measured three times on a computerized spirometer (Compact; Vitalograph; Buckingham, UK), and the best trial is reported. Spirometry was performed just before the inhalation of either the placebo or the FP. Cortisol was measured using an automated system based on a solid-phase chemiluminescent enzyme immunoassay (IMMULITE system; Diagnostic Products; Los Angeles, CA).

Data Analysis

The nocturnal cortisol production was calculated as the area under the curve using Simpson’s rule for data points spaced equidistantly.

Table 1—Patient Characteristics*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>28</td>
</tr>
<tr>
<td>Age, yr</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>32</td>
</tr>
<tr>
<td>Range</td>
<td>18–43</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
</tr>
<tr>
<td>Male</td>
<td>16</td>
</tr>
<tr>
<td>Asthma severity</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>11</td>
</tr>
<tr>
<td>Moderate</td>
<td>17</td>
</tr>
<tr>
<td>Smokers</td>
<td>2</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>26</td>
</tr>
<tr>
<td>Mean FEV1, % predicted, L</td>
<td></td>
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<tr>
<td>Before placebo</td>
<td>73.4</td>
</tr>
<tr>
<td>Before FP</td>
<td>71.3</td>
</tr>
</tbody>
</table>

*Data are expressed as No. unless otherwise indicated.

To compare the results obtained the night the placebo was used to the results obtained the night the active drug was used, the percent changes of cortisol production were analyzed using the Mann-Whitney U test.

RESULTS

FEV1 ranged from 42 to 96% of predicted normal values (mean ± SEM, 71.3 ± 2.9%) before the administration of FP. These data did not differ from the results obtained just before the inhalation of the placebo during the beginning of the first night.

The mean cortisol levels during the 2 nights of the study are displayed in Figure 1. A single dose of inhaled FP from the second night had a considerable effect on the early morning rise of cortisol secretion. When the nocturnal cortisol production after the second night was compared to that after the first night (when the placebo was administered), the total nocturnal cortisol production, calculated as AUC8h, was found to have significantly reduced by 29.4%. The individual changes in the nocturnal cortisol production are shown in Figure 2. There was a statistically significant correlation between the FEV1 measured just before the inhalation of FP and the fall in cortisol production ($p < 0.001$; Fig 3). There was no correlation between the FEV1 prior to the placebo and baseline cortisol production (as expressed by the AUC8h during the first night) or between the baseline cortisol production and the decrease in cortisol production during the second night.

DISCUSSION

This study has shown that in asthmatic patients, a single inhalation of FP causes a significant reduction in nocturnal AUC8h plasma cortisol. This reduction
was inversely correlated with the patient’s airway obstruction. The data suggest that there is a dose-response relationship with regard to the efficacy of IGC, at least in terms of conventional dosing regimens.\textsuperscript{2,3,10} IGC are generally regarded as safe at low doses. However, higher doses may not be without risk of toxicity. Growth retardation,\textsuperscript{11–15} dose-dependent suppression of the HPAA,\textsuperscript{6,16} adrenal insufficiency after discontinuation of chronic therapy,\textsuperscript{17,18} and abnormal effects on bone formation,\textsuperscript{19} bone turnover,\textsuperscript{20} and bone density\textsuperscript{21} have recently been reported.

It is likely that higher doses of IGC pose a greater risk for adrenal suppression; unfortunately, the doses at which the risk for adrenal suppression outweigh the beneficial effects of the drug are not known.

Systemic bioavailability of inhaled drugs may arise from absorption through the GI tract or the lung. Although buccal absorption of IGC is limited by the small absorptive surface area, a high degree of lipid solubility may enhance buccal absorption. Therefore, mouth rinsing following inhalation may reduce oral bioavailability.\textsuperscript{22,23} IGC absorbed from the intestine undergo an extensive degree of first-pass hepatic metabolism. While beclomethasone dipropionate may be transformed to active metabolites, the first-pass metabolism of the newer IGC, FP and budesonide, is 99% and 89%, respectively,\textsuperscript{24,25} with no known biotransformation to an active metabolite.

On the basis of this data, it can be inferred that the systemic bioavailability of IGC is mainly determined by the absorption across the lung vascular bed. Therefore, lung deposition would be expected to determine the systemic absorption and adverse effects of the drugs. Lung deposition of inhaled drugs depends on the delivery system used,\textsuperscript{8} the dose,\textsuperscript{7,22} and, potentially, the degree of airflow obstruction. Melchor and associates\textsuperscript{8} found that lung deposition of inhaled salbutamol was significantly higher in normal subjects than in patients with airflow obstruction, whatever the delivery system. Mean baseline FEV\textsubscript{1} was about 50% of predicted normal values, and lung deposition of the drug was about 75% of the amount of lung deposition in normal subjects. In other studies,\textsuperscript{26,27} significant airflow obstruction (mean FEV\textsubscript{1} = 56% of predicted normal values) was associated with an approximately 50% difference in peak plasma fenoterol concentration following drug inhalation (1.6 ng/mL vs 3.1 ng/mL).

Although increasing the steroid dose for patients with asthma is presumed to be associated with greater clinical efficacy and with higher incidence of systemic effects, clinically relevant dose-response relationships are difficult to prove. Some studies have shown a shallow dose-response relationship.\textsuperscript{28–30} On the other hand, greater incremental changes in efficacy variables at higher doses of IGC were reported by others.\textsuperscript{2,31} It is suggested, therefore, that the dose of IGC required to achieve optimal asthma control varies among patients, due to variations in tissue sensitivity to IGC, the severity of the underlying disease, and, as a logical assumption from the present study (at least for FP), its relation to the degree of airflow obstruction.

The clinical significance of our short-term observation of the effect of FP on the HPAA is unclear and should be elucidated in long-term studies. The correlation of such an observation with the systemic side effects of IGC is not clear. Other IGC should also be investigated. In addition, it should be noted

![Figure 2](http://publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21932/ on 06/16/2017)

**Figure 2.** The individual data of nocturnal cortisol production following inhalation of placebo and FP.

![Figure 3](http://publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21932/ on 06/16/2017)

**Figure 3.** The correlation between the FEV\textsubscript{1} just before the inhalation of FP and the fall in cortisol production.
that although our data may not represent total cortisol secretion, it may represent a delay in the peak cortisol secretion because we measured only overnight cortisol secretion until 6:00 AM. Because peak cortisol secretion occurs between 4:00 AM and 8:00 AM, optimally, the study should have continued until 9:00 AM or been conducted over an entire 24-h period.

Guidelines on asthma treatment generally recommend the administration of the lowest dose of IGC compatible with asthma control. It is known in general clinical practice that improved asthma control can be achieved by increasing the dose of IGC. Further studies are needed to quantify lung bioavailability of FP and other IGC in order to allow the clinician to optimize asthma control with the lowest risk for systemic adverse effects.

REFERENCES
9 American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987; 136:225–244
30 Dahl R, Lambie S, Malo JL. A dose ranging study of fluticasone propionate in adult patients with moderate asthma. Thorax 1993; 104:1352–1358
31 Costello JF, Clarke TJH. Response of patients receiving high dose beclomethasone dipropionate. Thorax 1974; 29:571–573