The effects of the inhaled corticosteroid budesonide on lung function and bronchial hyperresponsiveness in adult patients with cystic fibrosis


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Bronchial hyperresponsiveness is present in 40–60% of adult patients with cystic fibrosis (CF). Drugs which alter airway hyperresponsiveness have not yet been studied in CF. In this randomized placebo-controlled study, we investigated the effects of an inhaled corticosteroid, budesonide, on lung function and bronchial hyperresponsiveness in adult CF patients, with proven bronchial hyperresponsiveness to histamine. Twelve patients were treated with budesonide, 1600 μg day⁻¹, and with placebo during two periods of 6 weeks in a randomized, double-blind, cross-over study. Drug effects were assessed with regard to bronchial hyperresponsiveness to histamine, spirometry and clinical symptom scores. After treatment with budesonide, no significant differences in spirometry were seen, however, bronchial hyperresponsiveness to histamine significantly improved as compared to baseline. Fifty-eight percent of the patients showed at least one doubling-dose increase in PC_{20} histamine. Daily symptom scores showed small, but statistically significant, improvements in dyspnoea and cough after budesonide treatment. There is increasing evidence suggesting that excessive inflammatory responses contribute to the pulmonary damage that characterizes CF. Treatment with oral corticosteroids improved the clinical course of selected CF patients, but was associated with unacceptable adverse effects. We conclude that daily inhalation of 1600 μg day⁻¹ budesonide for 6 weeks induced a small, but significant, improvement in bronchial hyperresponsiveness to histamine, and symptoms of cough and dyspnoea in adult CF patients. Longer observations are needed to establish whether inhaled corticosteroids improve the long term outcome of CF.

Introduction

Bronchial hyperresponsiveness is a functional characteristic of bronchial asthma. Its presence can be demonstrated by assessing the bronchoconstrictor response to inhaled pharmacologic agents, such as histamine and methacholine. Patients with cystic fibrosis (CF) show this hyperresponsiveness to inhaled stimulants in 40–60% of cases (1–4). The mechanism of bronchial hyperresponsiveness in CF is unclear, although a relation with the underlying airway disease has been suggested (2). Existing airway narrowing and thickening of the airway wall may alter the airway geometry to such an extent, that a small increase in degree of narrowing produces a greater relative change in cross-sectional area (5). In addition, chronic inflammation may enhance the mucosal permeability and allow better penetration of histamine to bronchial smooth muscles and ‘irritant’ receptors (6). However, observations that FEV₁ is lower in hyperresponsive CF patients (2,4,7) than in non-hyperresponsive CF patients, are not confirmed by other authors (3,8). Others have suggested that airway hyperresponsiveness in CF is a genetically determined, systemic abnormality, associated with abnormal autonomic responses (9,10). Regardless of its cause, bronchial hyperresponsiveness in CF appears to be an unfavourable prognostic finding, as demonstrated in a prospective study in which the natural history of lung disease was more severe in hyperresponsive CF patients (2). In patients with allergic asthma, treatment with inhaled corticosteroids induces a clear change in bronchial hyperresponsiveness, expressed by increases in tolerance to histamine and ultrasonically nebulized distilled...
water, improvement of lung function and clinical symptom scores (11–13). Drugs which alter airway hyperresponsiveness have not yet been studied in CF.

In this randomized, placebo-controlled study, we investigated the effects of an inhaled corticosteroid, budesonide, on lung function and bronchial hyperresponsiveness in adult CF patients, with proven bronchial hyperresponsiveness to histamine.

Subjects and Methods

SUBJECTS

Sixteen CF patients (mean age 27 years; range 16–45 years) volunteered to participate in the study. The diagnosis CF was established by sweat test. All patients had a baseline FEV₁ above 25% of predicted values (14), absence of a recent (<6 weeks) acute pulmonary exacerbation and a PC₂₀ FEV₁ histamine below 16 mg ml⁻¹. Excluded were pregnant patients, patients who used oral corticosteroids or patients with severe concomitant disease which might interfere with the study and performing the tests. The study was approved by the hospital's Medical Ethics Committee, and written informed consent was obtained from all subjects.

METHODS

The study consisted of three periods. Period one was a run-in period of 2 weeks and periods two and three were double-blind, placebo-controlled, crossover medication periods of 6 weeks. At the first and last day of the run-in period, and at the last day of each treatment period, the patients underwent spirometry and a histamine provocation test. Inhaled bronchodilators were withheld for at least 12 h prior to each visit, while test medication was continued normally. Throughout the entire study, patients maintained a diary of symptoms and daily peak expiratory flow rate (PEFR) measurements. The best of three PEFR measurements was recorded twice daily, before medication use. On each day, scores for dyspnoea at rest and during exercise, cough and sputum production were recorded (0–3: 0=no complaints, 3=severe complaints). Only β₂-agonists were allowed to be used as bronchodilators if necessary, and their use was recorded. Prophylactic antibiotics, pancreatic enzymes and vitamin supplements when appropriate, were continued throughout the trial. Sodium cromoglycate, antihistaminics and theophylline preparations were stopped prior to the study protocol. Lung function tests were performed with a standard wet spirometer (Pulmonet III, Sensor-Medics, Bilthoven, The Netherlands). Allergy status was checked by RAST tests for 10 common inhalational allergens. Allergy was defined as at least one positive test result by the RAST method. Standardized histamine provocation tests were performed, and computerized calculations of the provocative concentration of histamine producing a 20% fall in FEV₁ (PC₂₀ histamine) were made (15). A pulmonary exacerbation of CF (defined as fever, increase in coughing and sputum production, weight loss, decrease in lung function and the need for antibiotic intervention) was reason for removal from the trial. Blinded, metered dose inhalers were supplied by ASTRA Pharmaceutics, Rijswijk, The Netherlands. The inhalers contained budesonide with 200 μg puff⁻¹, or placebo. Four puffs were inhaled two times a day via a spacer device (Nebuhaler).

STATISTICS

Diary card parameters and PEFR values were averaged over the 2 week run-in period, and over the last 2 weeks in the two treatment periods. The Wilcoxon test for paired differences was used on lung function data, log PC₂₀, mean PEFR and symptom scores. Five percent was taken as the level of significance. Data are expressed as mean ± SEM.

Results

Of the 16 patients who started the study, 12 patients provided complete data for analysis. Patient characteristics are given in Table 1. Two patients were withdrawn from the study because of non-compliance, both during placebo treatment. One patient was withdrawn from the trial after an acute infection with *Pseudomonas aeruginosa* during treatment.
Table 2  Effects of treatment with placebo and budesonide on lung function, symptom scores, daily peak flow expiratory rate and β₂-agonist use (puffs day⁻¹) in 12 adult patients with cystic fibrosis (mean values). P-values denote significant differences between values after placebo and values after budesonide. Baseline data represent values after the run-in period.

<table>
<thead>
<tr>
<th>Spirometry values</th>
<th>Baseline</th>
<th>Placebo</th>
<th>Budesonide</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (l)</td>
<td>2.3</td>
<td>2.2</td>
<td>2.3</td>
<td>NS</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>3.5</td>
<td>3.3</td>
<td>3.6</td>
<td>NS</td>
</tr>
<tr>
<td>MEF₂₀ (l min⁻¹)</td>
<td>1.7</td>
<td>1.7</td>
<td>1.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

Diary card scores (0-3)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Baseline</th>
<th>Placebo</th>
<th>Budesonide</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea at rest</td>
<td>0.47</td>
<td>0.54</td>
<td>0.38</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Dyspnoea on exercise</td>
<td>0.73</td>
<td>0.97</td>
<td>0.98</td>
<td>NS</td>
</tr>
<tr>
<td>Cough</td>
<td>1.19</td>
<td>1.20</td>
<td>1.14</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Sputum production</td>
<td>2.2</td>
<td>2.3</td>
<td>2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Morning PEFR (l min⁻¹)</td>
<td>433</td>
<td>416</td>
<td>421</td>
<td>NS</td>
</tr>
<tr>
<td>Evening PEFR (l min⁻¹)</td>
<td>449</td>
<td>442</td>
<td>443</td>
<td>NS</td>
</tr>
<tr>
<td>β₂-agonist use</td>
<td>1.2</td>
<td>1.2</td>
<td>1.1</td>
<td></td>
</tr>
</tbody>
</table>

with budesonide, whereas the fourth patient was withdrawn after a trauma (broken leg). The airways were colonized (≥ three sputum cultures) with Pseudomonas aeruginosa in eight patients (patient no. 1, 2, 4, 6, 7, 9, 11, 12), with Haemophilus influenza and Staphylococcus aureus in one patient (no. 5), with S. aureus alone in one patient (no. 8), whereas the remaining two patients (no. 3, 10) did not have bacterial colonization of their airways at the time of the study. Three patients (no. 8, 11, 12) used prophylactic antibiotics throughout the study. No patients started or stopped antibiotics during the trial.

The results of baseline spirometry before and after the 2 weeks run-in period were comparable within a 5% range. Also, the PC₂₀ histamine levels showed good reproducibility: Log PC₂₀ values were 0.22 ± 0.15 before, and 0.22 ± 0.18 at the end of the run-in period. During placebo treatment, no significant changes occurred in any of the spirometric values (Table 2). Also, mean Log PC₅₀ histamine after placebo was not significantly different from baseline.

After 6 weeks treatment with budesonide, small, but not significant, changes were observed in FEV₁ and FVC (Table 2). None of the patients showed an increase in baseline FEV₁ (l) of >15% after budesonide. The mean Log PC₂₀ histamine increased after budesonide from 0.22 to 0.50 mg ml⁻¹ (P<0.01). The geometric mean PC₂₀ histamine increased from 1.6 to 3.2 mg ml⁻¹, the difference being small but statistically significant. Seven patients showed at least one doubling dose increase in PC₂₀ histamine (Fig. 1). Of these seven patients, two were allergic.

Fig. 1 Individual data (•) and mean values (−) of PC₂₀ histamine levels (mg ml⁻¹) before and after 6 weeks of treatment with 1600 µg day⁻¹ budesonide in 12 adult CF patients.
No correlation was found between the improvement in $PC_{20}$ and the change in $FEV_1$, or with baseline $FEV_1$. Daily symptom scores, PEFR measurements and the use of $\beta_2$-agonists were collected from the diary cards. The mean diurnal variation of PEFR was 3.9% (range 0.3–8.9%) and did not change during treatment periods. None of the individual patients showed a diurnal variation of PEFR $>10\%$. A small improvement in the scores for dyspnoea at rest ($P=0.02$) and cough ($P=0.03$) could be observed after budesonide treatment in comparison with placebo (Table 2). The other parameters showed no significant differences between the two treatment periods. No significant differences were seen in the budesonide period when compared to placebo period, with respect to bacterial colonization, need for hospital admission and antibiotic therapy. No side effects were reported by the patients. Four patients were arbitrarily considered allergic. These four patients showed positive RAST tests to two or more inhalational allergens. These positive RAST tests were *Aspergillus fumigatus* (2), tree pollen (2), grass pollen (3), and house dust mite (2). No eosinophilia was present in the studied patients. No patient suffered from clinical allergy. The results of all tests were not significantly different between allergic and non-allergic subjects.

**Discussion**

The results of this study indicate that treatment with inhaled corticosteroids decreases bronchial hyperresponsiveness in adult patients with CF. This is the first study showing that the severity of bronchial hyperresponsiveness in CF patients can be decreased with anti-inflammatory therapy. In patients with asthma, long term treatment with inhaled corticosteroids showed clear improvement in bronchial hyperresponsiveness, lung function and clinical symptom scores (11, 12, 19, 20). The efficacy of inhaled corticosteroids is controversial in chronic obstructive pulmonary disease (COPD). Several studies have shown no significant improvement in $FEV_1$ or bronchial responsiveness to histamine, in an overall population of COPD patients treated with inhaled corticosteroids (16–18). In non-CF patients with bronchiectasis, lung function, cough and sputum production improved significantly after daily inhalation of 1500 $\mu$g beclometasone over 6 weeks (21). Treatment with inhaled sodium cromoglicate in CF patients showed no beneficial effects on symptoms, pulmonary function tests or methacholine responsiveness (22). Controlled trials using inhaled corticosteroids in CF patients have not yet been reported. A retrospective study showed some beneficial effects on lung function of treatment with inhaled steroids, as adjunct to antibiotics in selected CF patients during an exacerbation of airways infection (23). We performed a double-blind, placebo-controlled, cross-over trial with high dose budesonide and found a beneficial effect on bronchial hyperresponsiveness.

The decrease in $PC_{20}$ histamine was not accompanied by an increase in spirometric values. It is possible that the number of patients limited the statistical power of the trial to detect small changes. Daily symptom scores showed small, but significant, improvements in dyspnoea at rest, and in coughing. Seven of the 12 patients showed at least one doubling dose increase in $PC_{20}$ histamine. The improvement in $PC_{20}$ could not be attributed to improvement in bronchial calibre, because no correlation existed between the change in $PC_{20}$ and the change in $FEV_1$, if present. Although the observed beneficial effects of an inhaled corticosteroid on this group of adult CF patients were small, the results are encouraging. Whether a longer observation period than 6 weeks, and doses of budesonide above 1600 $\mu$g day$^{-1}$ would provide stronger beneficial effects on lung function, remains to be determined.

The attenuation of bronchial hyperresponsiveness without concomitant change in airway calibre, might reflect a decrease in epithelial permeability and/or the presence of inflammatory cells and mediators. Others have shown that in patients with CF, bronchial hyperresponsiveness is an unfavourable prognostic finding, associated with more rapid pulmonary deterioration (2). In the CF lung, elevated levels of neutrophil proteases, such as elastase, tumour necrosis factor and Interleukin-8 suggest a self-perpetuating inflammatory process on the bronchial surface (24, 25). Several data suggest the existence of an excessive inflammatory immune response in the lungs of CF patients (26). In this view, the use of the non-steroidal, anti-inflammatory drug ibuprofen was investigated in a rat model of chronic pseudomonas endobronchial infection. Ibuprofen significantly decreased the extent of the inflammatory response without increasing the pulmonary burden of bacteria (27). Following also the concept of hyperinflammation, several trials of immunosuppressive therapy using oral corticosteroids have been performed in CF patients. A short term trial of 0.5 mg kg$^{-1}$ prednisolone daily over 3 weeks in 15 CF patients with severe airflow obstruction, showed no significant improvement in spirometry or clinical condition (28). However, in a long term controlled study with 2 mg kg$^{-1}$ prednisolone on alternate
days, significant beneficial effects (better lung function, less hospital admissions) were seen in a group of 45 children with CF, aged 1–12 years (29). These results suggest that the corticosteroid therapy had modulated the excessive immune response. Unfortunately, longer follow-up of CF patients treated with oral corticosteroids showed a variety of important and unacceptable adverse effects, such as substantial growth retardation, early cataract formation and glucose intolerance (30,31). Therefore, at present, chronic oral corticosteroid treatment cannot be recommended.

In summary, there is increasing evidence to suggest that excessive inflammatory responses contribute, at least in part, to the pulmonary damage that characterizes CF. In this study of adult CF patients, we found that daily inhalation of 1600 µg budesonide for 6 weeks induced a small, but significant, improvement in bronchial responsiveness to histamine, and symptoms of cough and dyspnoea. Longer observations are needed to establish whether inhaled corticosteroids improve the long term outcome of CF.

References

