Effects of inhaled budesonide on spirometric values, reversibility, airway responsiveness, and cough threshold in smokers with chronic obstructive lung disease

B Auffarth, D S Postma, J G R de Monchy, Th W van der Mark, M Boorsma, G H Koëter

Abstract
Inhaled corticosteroids are known to reduce respiratory symptoms and airway responsiveness in allergic patients with asthma. The aim of the present randomised, double blind study was to assess the effect of eight weeks' treatment with inhaled budesonide in non-allergic smokers with chronic obstructive lung disease. Twenty four subjects (23 male) entered the study. Their ages ranged from 40 to 70 (mean 57) years, with a mean of 35 (range 9-80) pack years of smoking; the mean FEV₁ was 53% (range 32-74%) predicted and geometric mean PC₂₀ (histamine concentration causing a 20% fall in FEV₁) 0.96 (range 0.07-7.82) mg/ml. After a two week washout, single blind, placebo period, 12 patients were allocated to treatment with budesonide 1600 μg/day and 12 to placebo for eight weeks. The only additional drug to be taken was ipratropium bromide "if needed." Twenty one patients completed the study, 10 in the budesonide group and 11 in the placebo group. The standard deviation of the difference between duplicate measurements of PC₂₀ histamine and citric acid cough threshold made two weeks apart was below one doubling dose step. There was a significant reduction in dyspnoea in the budesonide group, but otherwise no change in symptom scores or use of ipratropium bromide over the eight weeks of treatment within or between the two groups. No significant differences in spirometric values, peak expiratory flow, PC₂₀ histamine, or citric acid cough threshold were found between the groups. Although differences were not significant, some of the changes showed a trend in favour of budesonide. Whether a longer observation period would show a significant influence of inhaled corticosteroids in patients with chronic obstructive lung disease remains to be determined.

Several investigators have shown that maintenance treatment with inhaled corticosteroids decreases airway responsiveness in patients with allergic asthma, possibly because of an effect on inflammatory processes within the airways.

The role of oral and inhaled corticosteroids in the treatment of smokers with chronic obstructive lung disease remains controversial, however. Short term treatment with oral corticosteroids caused no overall improvement in patients with chronic obstructive lung disease in several studies, but in some double blind crossover, placebo controlled studies "responders" were distinguished from "non-responders," one of the differences being a higher peripheral blood eosinophil count. Inhaled corticosteroids, such as beclomethasone dipropionate and budesonide, have a strong topical effect and far fewer systemic side effects than oral corticosteroids. There are only a few reports on the effect of inhaled corticosteroids on patients with chronic obstructive lung disease. In a recent study 14 of 24 patients with chronic obstructive lung disease responded, with a 10% or more increase in forced expiratory volume in one second (FEV₁) or forced vital capacity (FVC), or peak expiratory flow (PEF), to 1500 μg of inhaled beclomethasone dipropionate a day. In this study, however, some allergic individuals were also included, to judge by IgE values and skin test responses. Recently it has been suggested that little or no change in airway responsiveness occurs after 800 or 1200 μg of inhaled corticosteroids.

The aim of our study was to investigate the effects of treatment with a high dose of an inhaled corticosteroid on airflow obstruction, airway responsiveness, and cough threshold in current non-allergic smokers with moderate, partially reversible airflow obstruction.

Methods
PATIENTS
Twenty four patients (23 male), with a mean age of 57 (range 40-70) years, participated in the study. Inclusion criteria were: smoking at least one cigarette a day for at least five years; FEV₁ 30-75% predicted; reversibility, in terms of the difference between FEV₁ % predicted before and after 0.5 mg inhaled terbutaline, of less than 20%; a provocative concentration of histamine causing a 20% fall in FEV₁ (PC₂₀) of less than 16 mg/ml. Skin test responses to 12 common allergens and IgE
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specific for house dust mite had to be negative, total serum IgE had to be below 470 IU/ml, and the peripheral blood eosinophil count had to be below $0.2 \times 10^6$/l. The patients had no upper respiratory tract infection or any oral corticosteroids in the two months before the study. Inhaled corticosteroids were stopped two weeks before the start of the double blind study period.

STUDY DESIGN
Patients were seen in the outpatient department at two week intervals over 12 weeks. The first two visits were before and after a single blind placebo treatment period of two weeks (four puffs twice daily administered via the Nebuhaler, Astra). They were then allocated at random to one of two parallel groups in a double blind design. Twelve patients received 1.6 mg/day budesonide (four puffs twice daily via the Nebuhaler) for eight weeks; and the other 12 were treated with a placebo inhaler. Measurements of FEV1, response to 0.5 mg terbutaline, PC20 histamine, and citric acid threshold were carried out every two weeks for eight weeks. For controlling any symptoms the only bronchodilator drug allowed, besides the study drugs, was ipratropium bromide "as needed." All other bronchopulmonary medication was discontinued two weeks before entry to the study. Drug canisters were weighed at each visit to assess the patients' compliance. The protocol was approved by the hospital medical ethical committee and written consent from each patient was obtained.

DIARY CARDS
The patients made daily recordings of morning and evening expiratory peak flow (PEF; Mini Wright, best of three attempts) and scored the symptoms of coughing and dyspnoea on a 0–3 scale (0 = none, 3 = severe). Sputum volume was estimated on a 0–5 scale (0 = none, 5 = more than one coffee cup) and the number of ipratropium bromide puffs inhaled was recorded.

MEASUREMENTS
All medication was stopped 12 hours before each visit, which took place at the same time of day. Inspiratory slow vital capacity (VC) and FEV1 were measured with a water sealed spirometer (Lode BV, Groningen, The Netherlands). After baseline FEV1 measurements a histamine inhalation provocation test was carried out. When the FEV1 had returned to a value above 85% of the highest value on that day a citric acid cough challenge was performed. After this challenge VC and FEV1 manoeuvres were performed before and 20 minutes after inhalation of 0.5 mg terbutaline to assess reversibility. Whenever a fall in FEV1 occurred after the citric acid challenge, reversibility was measured when the FEV1 had returned to the baseline value. FEV1 was expressed as % predicted.19

PC20 histamine
Histamine challenge was performed by a modification of the method of De Vries20 with a Wiesbadener doppelinhaltor and an airflow of 8 l/min (output 0.12 ml/min, mean particle size less than 5 pm). Inhalation of phosphate buffered saline (PBS) was followed by doubling doses of histamine from 0.03 mg/ml until there was a 20% fall in FEV1, from the post-PBS value or the maximum dose of 16 mg/ml was reached. The inhalation took two minutes (during tidal breathing) with intervals of at least five minutes between doses. FEV1 was measured 30 and 90 seconds after each inhalation. PC20 was estimated by linear interpolations on a log dose-response plot.

Citric acid cough threshold
Citric acid was nebulised in the same way as histamine. After a control measurement with saline the subject inhaled doubling concentrations of citric acid diluted in saline (from 1 to 512 mg/ml) during tidal breathing for one minute. FEV1 was measured 30 and 90 seconds after each inhalation. The interval between doses was at least five minutes. The cough threshold was defined as the first concentration of citric acid that induced cough during inhalation, provided that the following concentration also led to cough. Cough was registered with a pressure transducer connected to the spirometer. When no cough occurred with the highest citric acid concentration the cough threshold was arbitrarily set at 1024 mg/ml.

Withdrawals
Eleven of the 12 placebo treated and 10 of the 12 budesonide treated patients completed the trial. One patient in the actively treated group (No 4) was admitted to hospital with congestive heart failure on visit 3. One patient in the placebo group (No 11) and one in the budesonide group (No 10) had to be withdrawn after visits 3 and 4 respectively, owing to a respiratory tract infection that required treatment with oral corticosteroids, bronchodilators, and antibiotics.

STATISTICAL ANALYSIS
Logarithmic transformation of PC20 histamine values and the citric acid threshold values was carried out before analysis. Reproducibility was assessed as the standard deviation (SD) of the difference between duplicate measurements (d):

$$\text{(SD)}^2 = \frac{\sum d^2}{2k},$$

where k is the number of patients.

Diurnal variability of PEF values was calculated for each day as (afternoon reading–morning reading/mean of the two readings) = 100%; the mean for seven days was then calculated.

Student's unpaired t test was used to compare values for the two treatment groups. Changes within each group were analysed by paired t test. Means symptom scores for two week periods were compared by Wilcoxon's signed rank test. A p value of 0.05 or less was
regarded as statistically significant. Values are presented as means with standard deviations in parentheses.

Results

Patients

The clinical characteristics of the patients are shown in table 1. There were no statistical differences between the two groups with regard to baseline FEV₁, FEV₁ % predicted, reversibility, PC₂₀ histamine, or citric acid cough threshold. Diurnal PEF variability in the run in period was low and did not differ between groups, the mean (SD) percentage variation being 9.9 (4.2) in the budesonide group and 8.5 (4.2) in the placebo group. Compliance, as measured by weighing the cannisters, was similar in the two arms of the study, ranging from 80% to 89% in the budesonide group and from 79% to 91% per two weeks of usage in the placebo group.

Spirometry

Individual values of FEV₁ % predicted during the trial, obtained after withdrawal of bronchodilators for 12 hours or more and before any challenge procedure, are shown in table 2. Spirometric values did not change significantly in either group in the two week run in period.

Table 2: Individual FEV₁ % predicted values during the trial

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Placebo: week</th>
<th>Patient No</th>
<th>1600 µg budesonide: week</th>
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<tr>
<td></td>
<td>0  2  4  6  8</td>
<td></td>
<td>0  2  4  6  8</td>
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<tr>
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<td>54 63 51</td>
<td>1</td>
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<tr>
<td>Mean</td>
<td>53.5 52.8 53.5 50.1</td>
<td>Mean</td>
<td>53.0 52.4 55.1 55.8 54.5</td>
</tr>
<tr>
<td>SD</td>
<td>13.0 12.7 13.0 12.1</td>
<td>SD</td>
<td>12.1 15.6 13.7 12.8 13.2</td>
</tr>
</tbody>
</table>
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The mean (SD) percentage change in FEV₁ % predicted over the eight weeks of treatment (from visit 2 to visit 6) was -3.4 (6.9) for the placebo group and +0.4 (3.3) for the budesonide group. These changes did not differ significantly between the two groups (p = 0.12). The mean absolute change in FEV₁ between visit 2 and visit 6 was -0.12 (0.23) litres (p > 0.05) for the placebo group and +0.015 (0.11) for the budesonide group—an increase that was just below significance (p = 0.098). The difference between the two groups was not significant.

VC improved over the eight weeks of treatment in both groups. Although the increase in the budesonide group was greater (0.29 (0.23); p = 0.08) than that in the placebo group (0.10 (0.43)), the difference was not significant.

REVERSIBILITY
There was no significant difference in reversibility, expressed as the difference between FEV₁ % predicted before and after 0.5 mg terbutaline, between the groups at any time. There were no significant change in reversibility after the eight weeks budesonide compared with the pretreatment values. The mean percentage change in FEV₁ before and after terbutaline treatment was 6.1 (2.5) and 7.4 (1.5) in the placebo group and 7.2 (4.4) and 6.5 (5.0) in the budesonide group.

REPRODUCIBILITY OF PC₂₀ HISTAMINE
The standard deviations of the difference in duplicate measurements for citric acid threshold and PC₂₀ histamine were 0.77 doubling doses (DD) and 0.96 DD respectively (comparison of values before and after the two weeks' single blind placebo period). Reproducibility, expressed in terms of doubling dose, after six weeks of placebo treatment was 0.82 DD for histamine and 1.5 DD for citric acid.

PC₂₀ HISTAMINE
The ratios of PC₂₀ histamine values after and before eight weeks' treatment with placebo and with budesonide are presented in the figure. No significant differences were seen over the eight weeks of treatment within or between the treatment groups. The ratio of PC₂₀ histamine after eight weeks to the initial value was above 1 for placebo and less than 1 for budesonide; the differences were just less than significant. The mean change in log₂ PC₂₀ histamine after eight weeks' treatment was +0.086 (0.054) mg/ml in the placebo group and -0.208 (0.348) mg/ml in the budesonide group.

CITRIC ACID COUGH THRESHOLD
The mean changes in log₂ citric acid threshold after eight weeks' treatment were -0.14 (0.45) DD for the placebo group and -0.18 (0.47) DD for the budesonide group. There were no significant changes within or between the two groups.

DIARY CARD
Morning and evening PEF and symptom scores (dyspnoea score, coughing, and sputum production) were analysed by comparing days 8–14 with days 43–74 (table 3). There were no significant changes except in the dyspnoea score, which improved significantly during budesonide treatment (p < 0.05), whereas it increased only slightly in the placebo group (p = 0.08 for budesonide versus placebo). The use of ipratropium bromide as needed increased slightly, but was similar in the two groups during the whole study.

Discussion
The present study was carried out in non-allergic current smokers with chronic obstructive pulmonary disease. We were unable to find a statistically significant effect of eight weeks' treatment with budesonide 1.6 mg/day on lung function, reversibility, PC₂₀ histamine, or citric acid threshold, to judge by the similarity between the treated group and the placebo group.

The improvement in FEV₁ almost reached significance after eight weeks of active treatment, so the question arises whether a longer treatment period would have shown a difference between the two groups. Symptom scores for dyspnoea but not for coughing and sputum production showed a significant improvement. Reduced dyspnoea may be the first indicator of a slow improvement in lung function that otherwise may need more time to become.

| Table 3  Diary card data (mean (SD) values): improvements during the trial up to the day the patient was in the trial (day 43–74 minus day 8–14) |
|---------------------------------|-----------------|-----------------|
|                                  | Budesonide (n=12) | Placebo (n=11)  |
| Peak expiratory flow (l/min):   |                  |                  |
| Morning                         | 2.83 (47.0)      | 2.0 (33.3)       |
| Evening                         | 1.3 (36.2)       | 5.7 (21.4)       |
| Dyspnoea (0–3)                  | 0.22 (0.30)      | 0.10 (0.61)      |
| Cough (0–3)                     | 0.24 (0.47)      | 0.15 (0.77)      |
| Sputum (0–5)                    | 0.03 (0.19)      | 0.33 (0.95)      |
| Ipratropium bromide (No of puffs/day) | 0.48 (1.75) | 0.65 (1.07)   |

*p < 0.05 within group (t test).
detectable. Symptom scores for cough and sputum production were low at the beginning of the study. This may explain why no further improvement could be achieved.

Measurement of the cough threshold after provocation with citric acid is used frequently to assess the antitussive effects of drugs.21-25 The citric acid cough threshold did not change significantly nor did the symptom score for cough. The reproducibility of PC_{20} histamine was good and that of the citric acid cough threshold acceptable. The standard deviation of the difference between repeated measurements two weeks apart in both groups and after 10 weeks in the placebo treated group was around one doubling dose. The reproducibility for PC_{20} histamine has been similar in some other studies, summarised by Cockcroft.26 The reproducibility of the citric acid cough threshold has not been assessed before.

In the present study we could not distinguish “responders” from “non-responders” in the actively treated group. This may be because patients with features that might favour a response to corticosteroids, such as spumum eosinophilia and allergy, were excluded.

The results of our study are in keeping with those of recently published short reports of a Danish and a British group that indicated no improvement or only a small improvement in lung function or airway hyperresponsiveness after treatment for three months with 0.8 mg and 1.2 mg budesonide daily.27-28 Effects may be smaller in smokers than in non-smokers or ex-smokers, as the ongoing deleterious effect of smoking may prevent a response.

There are other possible explanations for the lack of effect of high doses of inhaled budesonide in these patients. Firstly, corticosteroids are known to be potent anti-inflammatory drugs but, in contrast to the “allergic asthmatics,” where inflammation is dominated by eosinophils, neutrophilic infiltration has a major role in smokers.29-32 The two types of inflammation may react differently to treatment with corticosteroids and the duration of the treatment may have been too short to result in clinical improvement. On the other hand, most of our patients were longstanding middle aged smokers, and such a chronic inflammatory stimulus may need longer treatment than allergic stimuli in young asthmatic patients. This hypothesis may be supported by findings of Postma et al.30-34 who showed in a retrospective study that long term use of more than 7.5 mg prednisolone a day was associated with a slower decline in FEV_{1}, or even improvement in patients with chronic obstructive lung disease and moderate to severe airflow obstruction. The association with decline in FEV_{1} was, however, seen only after 6-24 months of follow up. Another explanation could be the relation between FEV_{1} and airway hyperresponsiveness. In allergic asthmatic patients FEV_{1} and airway hyperresponsiveness appear to be mainly independent phenomena: patients with normal baseline lung function may be very hyperresponsive. In smokers with chronic airflow obstruction the relation is stronger: in most studies the degree of airway hyperresponsiveness correlates with baseline FEV_{1}.35 Lim et al.36 found an increase in PC_{20} histamine after four years’ follow up of healthy smokers, in contrast to a stable PC_{20} in ex-smokers; the increase in PC_{20} in the smokers was associated with a fall in FEV_{1}, from 83% to 77% of the predicted FEV_{1}, whereas the FEV_{1} in the ex-smokers remained at 93% predicted.37

Taylor et al.38 did not find a significant correlation between the increase in white blood cell count and increased airway hyperresponsiveness in smokers and suggested that airway hyperresponsiveness and inflammation might not be causally related. If this is so it is not surprising that corticosteroids had little effect in our patients. The peripheral white blood cell count, however, is a very indirect marker of bronchial wall inflammation, as these authors mention. The hypothesis that inflammation and airway hyperresponsiveness are related in patients with chronic obstructive lung disease is therefore still not refuted.

In conclusion, we found that inhalation of 1.6 mg budesonide a day for eight weeks did not improve airway hyperresponsiveness as assessed by inhalation of histamine and citric acid. The increase in FEV_{1}, after eight weeks was just below significance, whereas the symptoms of dyspnoea improved significantly. The implication of this and other studies is that longer observation periods are required to establish whether inhaled corticosteroids have a beneficial influence on the outcome of chronic obstructive lung disease. Whether doses of budesonide above 1.6 mg would provide an earlier and better response, without side effects, is a further question that has to be answered.

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