Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma

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Background: Although inhaled corticosteroids have an established role in the treatment of asthma, studies have tended to concentrate on non-smokers and little is known about the possible effect of cigarette smoking on the efficacy of treatment with inhaled steroids in asthma. A study was undertaken to investigate the effect of active cigarette smoking on responses to treatment with inhaled corticosteroids in patients with mild asthma.

Methods: The effect of treatment with inhaled fluticasone propionate (1000 μg daily) or placebo for 3 weeks was studied in a double blind, prospective, randomised, placebo controlled study of 38 steroid naive adult asthmatic patients (21 non-smokers). Efficacy was assessed using morning and evening peak expiratory flow (PEF) readings, spirometric parameters, bronchial hyperreactivity, and sputum eosinophil counts. Comparison was made between responses to treatment in non-smoking and smoking asthmatic patients.

Results: There was a significantly greater increase in mean morning PEF in non-smokers than in smokers following inhaled fluticasone (27 l/min v –5 l/min). Non-smokers had a statistically significant increase in mean morning PEF (27 l/min), mean forced expiratory volume in 1 second (0.17 l), and geometric mean PC20 (2.6 doubling doses), and a significant decrease in the proportion of sputum eosinophils (~1.75%) after fluticasone compared with placebo. No significant changes were observed in the smoking asthmatic patients for any of these parameters.

Conclusions: Active cigarette smoking impairs the efficacy of short term inhaled corticosteroid treatment in mild asthma. This finding has important implications for the management of patients with mild asthma who smoke.
were three study periods, each of 3 weeks duration, during which subjects took inhaled placebo or fluticasone propionate (250 µg per puff) inhalers (metered dose inhalers via Volumatic spacer), two puffs twice daily according to randomisation. The patients were separated into smokers and non-smokers, with recruitment continuing in parallel for each group. At each study visit the PEF diary was retained, spirometric tests were performed, and a methacholine challenge test was carried out followed by sputum induction. The order of randomisation was such that, following a placebo run in of 1 week, each subject took either placebo or fluticasone propionate for 3 weeks followed by a placebo washout period of 3 weeks and a further 3 week period of placebo or fluticasone propionate. The order of treatment and placebo was balanced to minimise any order effect.

**Measurements**

**Peak expiratory flow (PEF) recordings**

PEF measurements were undertaken by patients at home using a mini-Wright peak flow meter (Clement Clarke, Harlow, UK). The best of three measurements was recorded twice daily (pretreatment) in the diary. Values of morning and evening PEF were averaged from the last 7 days before each study visit.

**Spirometry**

Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were measured with a dry spirometer (Vitalograph Ltd, Buckingham, UK) and the best of three attempts was taken for analysis. FEV1 was measured before and after 20 minutes after 200 µg salbutamol to test reversibility on the first visit.

**Bronchial hyperreactivity**

Bronchial challenge testing was undertaken using the technique described by Cockcroft et al.16 In summary, methacholine was administered by nebulisation in doubling doses with measurement of spirometric parameters at each dose using a protocol and equipment standardised in our laboratory. Quantification of the response was calculated by linear interpolation and expressed as the provoking concentration of methacholine required to produce a 20% fall in FEV1 (PC20 methacholine).

**Sputum induction**

Sputum induction was performed using a modification of the method described by Pin et al.17 Briefly, after salbutamol 200 µg was administered by metered dose inhaler with large volume spacer, sputum induction was started using hypertonic (3%) saline administered via an ultrasonic nebuliser (Medix Ltd, UK) over a period of 20 minutes. The subjects were encouraged to expectorate at any time throughout the procedure and, in addition, inhalation was stopped every 5 minutes to allow expectoration and to allow spirometric tests to be carried out. The sample was collected in a sterile container and transferred to the laboratory on ice as soon as possible, and in all cases in less than 2 hours. The protocol dictates that, if FEV1 falls by more than 20%, the procedure is discontinued, although no subject in this study required discontinuation. All samples were processed without the laboratory staff being aware of the clinical information relating to the individual subject, and the procedure followed was similar to that described by Popov et al.18 Sputum samples were transferred to a Petri dish and the volume and macroscopic characteristics of the whole sample were recorded. Sputum plugs were selected to minimise salivary contamination,19 and treated with 4× volume of fresh 0.1% dithiothreitol (DTT) (Sputolysin; Calbiochem-Novabiochem (UK) Ltd, Nottingham, UK) in distilled water. Following incubation with DTT for 20 minutes the DTT treated samples were filtered through 50 µm mesh (R Cadoch & Sons, London, UK) to remove residual mucus clumps and a total cell count was made using a white cell counter (CBC5, Coulter Electronics Ltd, UK). An aliquot was removed, diluted to 10× cells/ml in phosphate buffered saline, and cytocentrifuged (500 rpm for 5 minutes) using a Shandon centrifuge. Differential cell counts were made from the resulting slides using Giemsa staining and expressed after exclusion of squamous epithelial cells which are taken to represent salivary contamination.19

**Serum cotinine and total IgE**

Ten ml venous blood was drawn and centrifuged prior to analysis of serum cotinine and total IgE. Serum cotinine was assayed by a commercially available enzyme linked immunosorbent assay (Cozart Biosciences, Abingdon, UK) and total IgE (international units/ml) by enzymatic immunoassay (Unicap System, Pharmacia, Uppsala, Sweden).

**Assessment of compliance**

Compliance was assessed by weighing inhalers on their return following each treatment period.

**Statistical analysis**

The intended power of the study was 80% (at the 5% level) to detect a mean treatment difference in PEF of 35 l/min with a standard deviation in non-smoking asthmatics of 40 l/min. Non-parametric statistics were used (Mann-Whitney U test) for comparisons of change in PEF and sputum eosinophil proportions, since these data were not normally distributed. The Student’s t test was used to compare demographic and spirometric data. Bronchial hyperreactivity data were log transformed before analysis and are reported as geometric mean and geometric SD. Two types of analysis were performed: firstly, a comparison between smokers and non-smokers of changes across a particular treatment period (fluticasone propionate or placebo), assessing each treatment period therefore by measuring the change in values obtained immediately before and immediately after that particular treatment; and, secondly, a comparison across groups of the effect of fluticasone (fluticasone-placebo) in smokers and non-smokers. Significance was accepted at a level of p<0.05.

**RESULTS**

**Baseline patient characteristics**

Following screening for bronchial hyperreactivity and bronchodilator reversibility, 47 patients were enrolled into the study. Nine patients dropped out (all smokers) citing inconvenience in attendance as the main reason, leaving 38 patients for analysis (fig 1). There were no significant differences between smoking and non-smoking asthmatic patients at baseline in terms of age, duration of asthma, total serum IgE, FEV1, % predicted, bronchodilator reversibility, bronchial hyperreactivity (geometric mean PC20 methacholine), or baseline morning and evening PEF % predicted (table 1). Smoking asthmatics had higher mean (SD) serum cotinine levels than non-smokers (125.7 (13.1) mg/l v 11.4 (8.4) mg/l; p<0.0001).

**Baseline measurements and comparison of change across treatment periods**

**PEF readings**

There was no difference in baseline PEF measurements (% predicted) between non-smokers and smokers. In the non-smoking group the mean (95% CI) morning PEF increased from baseline by 27 (14.4 to 39.6) l/min following fluticasone and by 14 (–2.4 to 30.6) l/min following placebo (fig 2, table 2, p=0.016). In the smoking group the mean (95% CI) morning PEF decreased by –5 (–17.7 to 7.8) l/min following fluticasone and by 0 (–8.5 to 9.0) l/min following placebo (fig 2, table 2, p>0.05). There was a significantly greater

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change in morning PEF in non-smokers than in smokers following inhaled fluticasone (p=0.006). Evening PEF was not significantly affected by inhaled fluticasone in either group, although there was a trend towards a greater change in the non-smoking group than in the smoking group (p=0.051).

**Spirometry**

In the non-smoking group the mean (95% CI) % predicted FEV1 increased from baseline by 5% (0.9 to 8.5) following fluticasone, compared with a geometric mean (95% CI) increase of –0.05 l (–0.18 to 0.07) following placebo (p=0.006). The change in the magnitude of change in methacholine PC20 following inhaled fluticasone (no significant difference). The change in sputum eosinophils following inhaled fluticasone was not significantly different in non-smoking and smoking asthmatic patients.

**Comparison between end of placebo and fluticasone treatment periods**

No significant changes in FEV1, PEF, methacholine PC20, or sputum eosinophils were found between the values at the end of the treatment periods.
Table 2  Mean (95% CI) changes in lung function and induced sputum eosinophil counts during each treatment period

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Fluticasone</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smokers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEF (l/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morning</td>
<td>+14 (2.4 to 30.7)</td>
<td>+27 (14.4 to 39.6)</td>
<td>0.016</td>
</tr>
<tr>
<td>Evening</td>
<td>+2 (-11.8 to 17.2)</td>
<td>+16 (2.7 to 29.5)</td>
<td>0.051</td>
</tr>
<tr>
<td>FEV1 (l)</td>
<td>-0.05 (-0.18 to 0.07)</td>
<td>+0.17 (0.04 to 0.31)</td>
<td>0.01</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>-1 (-4.3 to 2.2)</td>
<td>+5 (0.9 to 8.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Geometric mean methacholine PC20 (mg/ml)</td>
<td>-0.07 (-0.7 to 0.9)</td>
<td>+1.3 (0.3 to 6.3)</td>
<td>0.0002</td>
</tr>
<tr>
<td>% sputum eosinophils *</td>
<td>0 (-0.7 to 2.5)</td>
<td>-1.8 (-6.6 to 2.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>Smokers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEF (l/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morning</td>
<td>0 (-8.5 to 9.0)</td>
<td>-5 (-17.7 to 7.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Evening</td>
<td>1 (-16.5 to 19.4)</td>
<td>0 (-8.5 to 9.0)</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1 (l)</td>
<td>-0.02 (-0.18 to 0.13)</td>
<td>-0.06 (-0.23 to 0.11)</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>-1 (-5.7 to 4.7)</td>
<td>-1 (-5.8 to 3.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Geometric mean methacholine PC20 (mg/ml)</td>
<td>-0.3 (-2.4 to 2.3)</td>
<td>-0.3 (-1.5 to 6.1)</td>
<td>NS</td>
</tr>
<tr>
<td>% sputum eosinophils *</td>
<td>0 (-0.5 to 1.4)</td>
<td>0 (-2.9 to 3.7)</td>
<td>NS</td>
</tr>
</tbody>
</table>

PEF = peak expiratory flow; FEV1 = forced expiratory volume in 1 second; PC20 = concentration of methacholine provoking a fall in FEV1 of 20% or more.

*Median values.

p values relate to comparison between placebo and fluticasone propionate for magnitude of change.
Pedersen et al. studied the responses to inhaled budesonide in asthma in a longer term study and found improvements in FEV1 and blood markers of inflammation which were not observed in a subgroup of smokers. The study was not placebo controlled, airway inflammation was not assessed directly, and the subgroup of asthmatic smokers studied had more severe airflow limitation than in the current study both before and after treatment. Our results are consistent with the findings of Pedersen’s study, with additional direct information on airway inflammation and the additional validation of a placebo control. The asthmatic patients in our study had mild asthma and had relatively low cigarette exposure (mean 16.5 pack years), suggesting that the lack of effect of inhaled corticosteroids in smokers does not depend primarily on the severity of asthma or the extent of cigarette exposure. It seems unlikely that any lack of response in smokers could be attributed solely to an insufficient dose of inhaled corticosteroid, in view of the response of the non-smokers and the published evidence that fluticasone is effective at much lower doses than those used in this study. 23 It has been shown that clinically significant effects of treatment are apparent after one day of treatment, and that smoking cessation in asthma, even in patients with mild disease, is likely to improve outcome. It is likely that patients with asthma should be encouraged to stop smoking, even if this is not sufficient to reverse the effects of smoking.

The mechanism behind the lack of response to inhaled corticosteroids in smoking asthmatics is not known. Cigarette smoke has the potential to cause harm to the airways in a number of ways, including direct toxicity and proinflammatory activity. Cigarette smoke contains a number of substances which can irritate the airways, including nitrogen dioxide, formaldehyde, acrylamide, and polycyclic aromatic hydrocarbons. 24 In the context of smoking-related inflammatory responses in healthy adults, the mechanism behind the lack of response to inhaled corticosteroids in smoking asthmatics is not known. Cigarette smoke contains a number of substances which can irritate the airways, including nitrogen dioxide, formaldehyde, acrylamide, and polycyclic aromatic hydrocarbons.

The British Thoracic Society guidelines for the monitoring of chronic obstructive pulmonary disease recommend that patients should be encouraged to stop smoking, even if this is not sufficient to reverse the effects of smoking. 25 In the context of smoking-related inflammatory responses in healthy adults, the mechanism behind the lack of response to inhaled corticosteroids in smoking asthmatics is not known. Cigarette smoke contains a number of substances which can irritate the airways, including nitrogen dioxide, formaldehyde, acrylamide, and polycyclic aromatic hydrocarbons.

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REFERENCES