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A trial of inhaled budesonide on airway responsiveness in smokers with chronic bronchitis

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A trial of inhaled budesonide on airway responsiveness in smokers with chronic bronchitis. T. Engel, J.H. Heinig, O. Madsen, M. Hansen, E.R. Weeke.
ABSTRACT: The aim of the present randomized, double-blind study was to evaluate the effect of inhaled budesonide on daily symptoms, ventilatory capacity, and airway responsiveness in smokers with chronic bronchitis. Twenty five subjects with a provocative concentration producing a 20% fall in forced expiratory volume in one second $PC_{20}(FEV_1)$ less than 2.0 $mg \cdot ml^{-1}$, by bronchial histamine challenge, were included. Eighteen subjects accomplished the entire 12 week study, eight receiving inhaled budesonide 400 μg *b.i.d.* and ten receiving placebo. Cough decreased significantly in the actively treated group during the treatment period, but no change could be demonstrated in expectoration, dyspnoea, or sleep disturbances. No changes in any of these symptoms were found in the placebo group, and no differences in symptoms scores were found between the groups. No significant differences in ventilatory capacity or bronchial responsiveness could be demonstrated. In conclusion, a moderately high dose of inhaled steroid in eight subjects with chronic bronchitis did not improve the symptom scores, ventilatory capacity, or airway responsiveness to any clinically relevant degree.
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One of the characteristic features of asthma is the increased sensitivity of the airways to extrinsic stimuli, *e.g.* cold air or histamine [1], which can be reduced by steroids [2]. Bronchial hyperresponsiveness is also known to occur in subjects with chronic bronchitis and normal ventilatory capacity, although to a minor degree [3–8]. Earlier studies of subjects with chronic bronchitis have investigated the efficacy of steroids in severe bronchial obstruction [9, 10]. We have been unable to find any published detailed results on the effect of inhaled steroids on hyperresponsiveness in subjects with chronic bronchitis and normal ventilatory capacity. However, a recently published abstract [11], showed no effect of budesonide.

The aim of the present study was to evaluate the effect of inhaled budesonide 400 μg *b.i.d.* on daily symptoms, ventilatory capacity, and airway responsiveness in subjects with chronic bronchitis, forced expiratory volume in one second (FEV_1) above 70% predicted, and bronchial hyperresponsiveness.

Materials and methods

Design

The study was performed in a randomized, double-blind, placebo-controlled fashion. After a 2 week run-in period, the subjects were randomized to receive either budesonide 400 μg *b.i.d.* by inhalation through a 750 ml spacer (Nebuhaler®), or placebo canisters which appeared identical, during a 12 week study period (fig. 1). The subjects registered severity of the following symptoms daily in a diary: cough, dyspnoea, sputum, and nightly sleep disturbances due to pulmonary causes (table 1). Peak expiratory flow (PEF) was measured twice daily, throughout the run-in period and the entire 12 week study period, on a mini Wright peak flow meter (Airmed, Clement Clarke International Ltd, London, UK), the best of three attempts being recorded. Measurements of ventilatory capacity and bronchial histamine challenge were performed every fourth week during the study period (fig. 1).

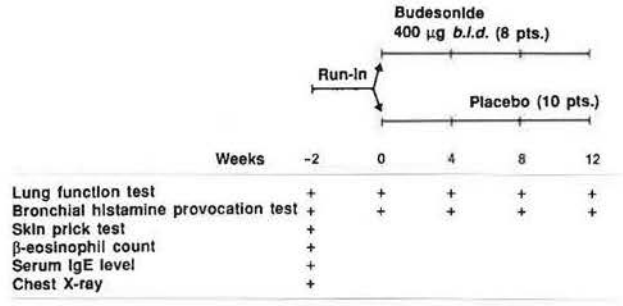

Fig. 1. – Study design.

Table 1. – Symptom scores recorded in diaries

Symptom score:	0	1	2	3
Cough	None	Few coughs every day	Repeated cough attacks, but only in the morning or during the day	Persistant cough attacks during the day and night
Expectoration	None	Sputum easily expectorated	Difficulties in bringing up sputum	Impossible to bring up sputum
Dyspnoea	None	Dyspnoea from climbing one floor	Dyspnoea from walking on plain level	Dyspnoea at rest
Nightly sleep disturbance due to pulmonary causes	None	Awake once per night	Awake 2–3 times per night	Awake ≥4 times per night

Table 2. – Descriptive data prior to the run-in period for the 18 subjects

	Budesonide	Placebo
Number of subjects	8	10
Age yrs	50.9 (37–57)	49.9 (43–58)
Sex M/F	2/6	6/4
Tobacco pack-years	33.3 (23–53)	36.6 (19–54)
FEV_1 *l*	2.32 (1.57–3.06)	2.81 (1.73–4.88)
FEV_1 % pred	96.9 (74–128)	97.7 (78–126)
FEV_1/FVC %	72 (56–95)	73 (55–84)
PEF home measurements* % pred (morning)	82.6 (58.5–130.1)	89.4 (78.1–99.5)
PEF home measurements* % pred (evening)	87.2 (55.8–118.3)	91.3 (75.2–104.6)
$PC_{20}(FEV_1)$ $mg \cdot ml^{-1}$	0.54 (0.23–1.10)	0.75 (0.20–1.65)

All data are arithmetic means except PC_{20} data, which are geometric means (range in parentheses). *: arithmetic mean of the 2 week run-in period; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; PEF: peak expiratory flow; $PC_{20}(FEV_1)$: provocative concentration producing a 20% fall in FEV_1.

Subjects

Twenty five subjects with chronic bronchitis, defined as cough and expectoration for at least three months a year during at least the preceding two years [12], and moderate to severe bronchial hyperresponsiveness as judged by a bronchial histamine challenge (provocative concentration producing a 20% fall in forced expiratory volume in one second $PC_{20}(FEV_1) \leq 2.0$ mg histamine$\cdot ml^{-1}$) were selected from a previous study [3]. All subjects were current tobacco smokers, 30–60 yrs of age, with a daily consumption of at least five cigarettes or a corresponding amount of pipe tobacco, cigarillos or cigars. All had an $FEV_1 \geq 70\%$ predicted [13] and normal chest X-ray. None had a history of asthma as defined by SCADDING [14] or allergic rhinitis, or had had an airway infection during the last six weeks. None had a positive skin prick test with the ten most common inhalant allergens in Denmark (SoluPrick®, ALK, Copenhagen, Denmark), [15], elevated number of blood eosinophils ($>400 \times 10^6 \cdot l^{-1}$ whole blood), or increased plasma immunoglobulin E (IgE) (>100 $kU \cdot l^{-1}$). None had ever been treated with inhaled or systemic glucocorticoids.

Four subjects were excluded during the run-in period because of lack of time or failure to attend the clinic at the scheduled time, and two for other reasons. Nineteen subjects completed the study. The weight of the returned medication canisters indicated that one subject had used less than half of the prescribed dose, and this subject was, therefore, omitted from the statistical analysis. The remaining subjects had used the recommended dose of study medication. The material, therefore, consists of 18 subjects, eight receiving budesonide and ten placebo (table 2).

Subjects were included in the study during the months December–March, and were thus followed until June. During the study, one subject in the placebo group experienced an exacerbation which was treated with mucolytics. The subject continued taking the study medication during the exacerbation; histamine challenge was not performed until six weeks after the exacerbation.

Ventilatory capacity

Measurement of the ventilatory capacity included forced expiratory volume in one second (FEV_1) and forced vital

capacity (FVC), and was carried out on a recently calibrated dry-wedge spirometer (Vitalograph Ltd, Buckingham, UK). All manoeuvres were repeated until three consecutive measurements showed a variation of 5% or less, or a maximum of eight attempts was reached. The largest value obtained was used in the subsequent analysis.

Bronchial histamine challenge

Tobacco was withheld prior to the challenge as recommended by the Societas Europaea Physiologiae Clinicae Respiratoriae (SEPCR) working group [16]. No subject used any medication known to interfere with the bronchial histamine challenge during the study period. The challenge was performed with a jet nebulizer-Pari Inhalier boy, airflow 11 $l \cdot min^{-1}$, output 0.27±0.03 $ml \cdot min^{-1}$ (mean±SD) (measured at the Allergy Clinic), particle size 0.5–5.5 μm (manufacturer's declaration). Inhalations were performed for 2 min with a 5 min interval. After inhaling isotonic saline, the subjects inhaled increasing doses of unbuffered histamine dihydrochloride, alternating with measurement of the ventilatory capacity 90 s after termination of inhalation. If a 20% decrease in FEV_1 had not yet been obtained, the test was discontinued after inhalation of histamine dihydrochloride 8 $mg \cdot ml^{-1}$ [17]. The result was expressed as the concentration of histamine causing a 20% decrease in FEV_1 compared to the FEV_1 value after inhaling isotonic saline ($PC_{20}FEV_1$) using interpolation on the log dose response curve. Values above 8 $mg \cdot ml^{-1}$ were reported as 8 $mg \cdot ml^{-1}$, no values below 0.125 $mg \cdot ml^{-1}$ were obtained.

Statistics

Unless otherwise stated, all results shown are arithmetic mean±SD. Statistical analysis was performed using Student's t-test, paired or unpaired as appropriate. All PC_{20} (FEV_1) values were logarithmically transformed prior to statistical analysis.

Results

Cough decreased significantly in the budesonide group after the 8–12 week study period when compared to the run-in period ($p<0.05$, paired t-test) (fig. 2). No differences in the placebo group were found ($p>0.05$, paired t-test), and no differences between the budesonide and the placebo groups could be demonstrated ($p>0.05$, unpaired t-test). None of the remaining symptoms, sputum, dyspnoea, or nightly disturbances from pulmonary causes, showed significant differences between the groups ($p>0.05$, unpaired t-test) or changes as compared to the run-in period ($p>0.05$, paired t-test).

There was no significant difference in FEV_1% between the budesonide and the placebo groups prior to the start of therapy or after 4, 8 and 12 weeks' study period ($p>0.05$, unpaired t-test) (fig. 3). No changes in either the budesonide or the placebo groups during the study could be demonstrated ($p>0.05$, paired t-test). Home peak expiratory flow (PEF) measurements (% predicted) showed no differences between the groups ($p>0.05$, unpaired t-test) (fig. 4). No subjects demonstrated a 20% or greater daily fluctuation in home measurement of PEF.

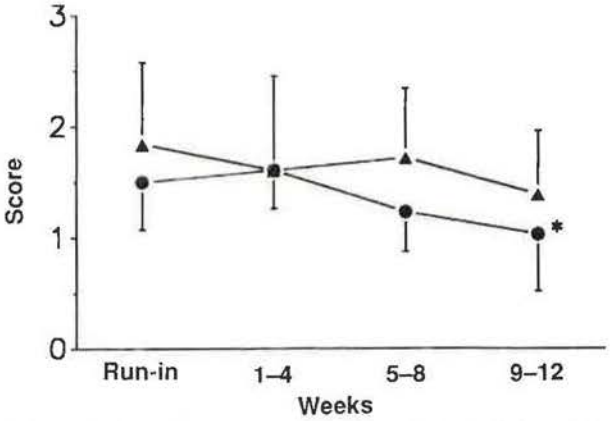

Fig. 2. – Cough symptom scores in 18 subjects with chronic bronchitis, treated with budesonide (●) or placebo (▲), arithmetic mean and SD (error bars). *: different from the run-in period ($p<0.05$).

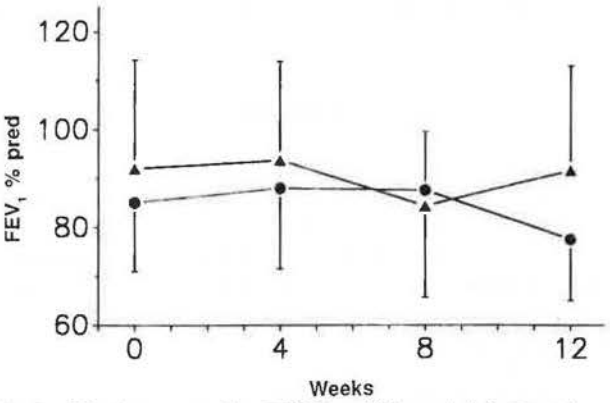

Fig. 3. – Ventilatory capacity (FEV % pred) (mean±SD) in 18 subjects with chronic bronchitis, treated with budesonide (●) or placebo (▲). FEV_1: forced expiratory volume in one second.

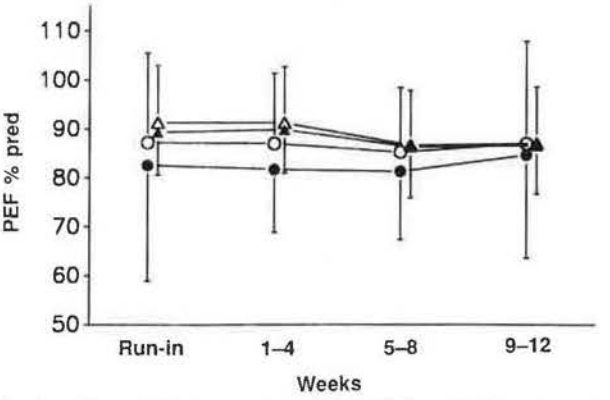

Fig. 4. – Home PEF measurements (% pred), best of three attempts, arithmetic mean±SD. Circles: budesonide group; triangles: placebo group; filled symbols: morning values; open symbols: evening values; PEF: peak expiratory flow.

Comparison between the budesonide and the placebo groups revealed no difference in PC_{20} (FEV_1) before the start of therapy or after 4, 8, and 12 weeks' study period ($p>0.05$, unpaired t-test) (fig. 5). Neither the budesonide group nor the placebo group showed significant alterations in $PC_{20}(FEV_1)$ after 4, 8 and 12 weeks' therapy (all $p>0.05$, paired t-test).

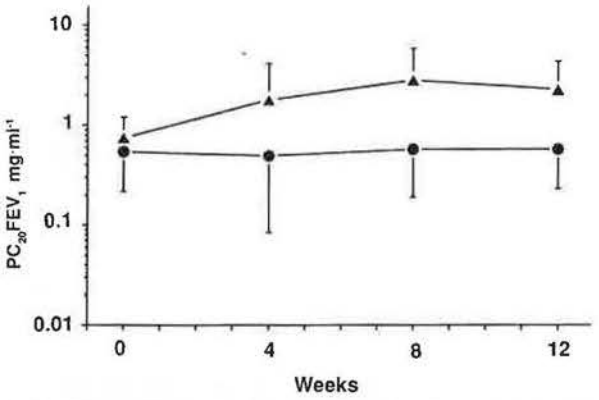

Fig. 5. – Degree of bronchial responsiveness, $PC_{20}(FEV_1)$, (mean log_{10}, bars indicate SD of log_{10}) in the 18 subjects with chronic bronchitis, treated with budesonide (●) or placebo (▲). PC_{20} FEV_1: provocative concentration producing a 20% fall in forced expiratory volume in one second.

Discussion

Treatment with inhaled glucocorticoids is well-established in chronic asthma, where it has been shown to reduce the nonspecific bronchial hyperresponsiveness [2, 18–20]. However, not all asthmatics respond equally well to steroid therapy [21]. Steroids are thought to reduce the inflammation in the bronchial wall of the asthmatic, although the mechanisms by which they act are still uncertain [22].

Eight to twelve weeks after the start of therapy we found a slight, beneficial effect of budesonide with respect to cough compared to the run-in period. Cough was the only symptom which decreased significantly.

Measurements of ventilatory capacity performed at the Allergy Clinic (FEV_1, FVC) and home measurements of PEF showed no improvement and no difference between the groups. FEV_1 was above 70% in all subjects prior to start of the study, and mean PEF was above 70% during the run-in period in all but three subjects in the budesonide group. Increases could, therefore, hardly be expected. There was a trend towards higher values for FEV_1 and PEF in the placebo group at inclusion, which was, however, abolished when calculated as % predicted; this was probably due to the high percentage of women in the budesonide group. These results parallel those recently published by WATSON *et al.* [11].

Neither the budesonide nor the placebo group showed any significant improvement with respect to bronchial responsiveness. The dose of budesonide given was higher than that given to asthmatics in earlier studies, where an effect was demonstrated [2, 19, 20], so underdosing is not likely to have occurred. Only 18 of the 25 subjects accomplished the entire study, and bias in the selection may, therefore, occur. No significant differences between the subjects accomplishing the study and the drop-outs were registered regarding bronchial responsiveness, FEV_1 % predicted, smoking habits, age and sex. Increasing the number of subjects is not likely to change the results, demonstrating an effect of inhaled budesonide on hyperresponsiveness, since only the placebo group showed a trend towards decreased responsiveness ($p=0.055$) (fig. 5).

In order not to overlook any possible effect, the study period was chosen as 12 weeks. The great variances in symptoms over the seasons of the year and the risk of exacerbations would probably make the results of a 24 week cross-over design unreliable. Our study period ran into the spring, which might explain the trend towards decreased responsiveness in the placebo group. This does not, however, explain why we found no effect on ventilatory capacity or hyperresponsiveness in the budesonide group.

The pathogenesis of hyperresponsiveness in asthma and chronic bronchitis may be of a different nature. Chronic bronchitis is dominated by hyperplasia of goblet cells and mucous glands, partial bronchial obstruction due to sputum and epithelial hyperplasia, and a reduced number of cilia. Steroids are reported not to have any effect on mucociliary clearance in chronic obstructive bronchitis [23].

In conclusion we found a decreased cough score in eight subjects treated with inhaled budesonide 800 μg daily for 12 weeks. No clinically relevant differences in ventilatory capacity, PC_{20} (FEV_1), home measurement of PEF, or symptom scores regarding dyspnoea, sputum, and nightly sleep disturbances were found. Our results, therefore, do not support the use of inhaled steroids in subjects with chronic bronchitis, FEV_1 above 70%, and bronchial hyperresponsiveness, unless cough is a predominant symptom.

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Comparison de la réactivité des voies aériennes chez les fumeurs bronchitiques et chez les asthmatiques. T. Engel, J.H. Heinig, O. Madsen, M. Hansen, E.R. Weeke.

RÉSUMÉ: Une hyperréactivité bronchique, exprimée en PC_{20} VEMS après provocation par inhalation d'histamine, a été retrouvée chez 52 de 95 fumeurs dont le VEMS est supérieur à 70% des valeurs prédites, mais qui sont atteints de bronchite chronique. Le degré de réactivité était systématiquement inférieur à celui trouvé chez les asthmatiques pairés, mais nettement supérieur à celui observé chez les sujets normaux. Le degré d'hyperréactivité est en corrélation significative avec les valeurs de base de la capacité ventilatoire, l'âge et la consommation de tabac, mais sans rapport avec le sexe. PC_{40} MEF_{50} a montré le même type de distribution que PC_{20}VEMS, mais n'a pas ajouté d'information complémentaire. La pente de la courbe dose-réponse du MEF_{50} n'a de corrélation avec aucun des paramètres mesurés. La pente des courbes dose-réponse du VEMS, par contre, montre une corrélation significative avec la consommation de tabac. Il y aurait lieu d'investiguer dans quelle mesure le degré d'hyperréactivité bronchique pourrait constituer un indice d'incapacité future.
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