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ORIGINAL ARTICLES

The Effects of Inhaled Corticosteroids on Chronic Airflow Limitation

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SUMMARY A placebo-controlled, double blind, cross-over study of inhaled budesonide was carried out to examine its effectiveness in the treatment of chronic airflow limitation (CAL). Fourteen patients (11 males, mean age 66 years) with stable CAL received placebo treatment for four weeks followed by inhaled budesonide 400 μg BD for eight weeks. Response was assessed by measuring forced expiratory volume in one second (FEV1). There was no significant improvement in the overall spirometric measurements and symptom scores except a reduction in daily peak expiratory flow rate fluctuation ($p < 0.05$). However, individual patients showed significant increase in FEV1. Two patients (14%) had greater than 30% increase in FEV1 in response to inhaled corticosteroids. This response could not be predicted from history of allergy, skin test, bronchial challenge test, peripheral blood or sputum eosinophilia. We conclude that only a minority of patients with stable CAL may respond to inhaled budesonide. Nontheless, patients who are symptomatic despite treatment with maximum doses of bronchodilators may have a trial of inhaled corticosteroids in order to demonstrate any additional benefit.

A number of studies on the effect of oral steroids in high doses on patients with 'irreversible' chronic airflow limitation (CAL) have produced conflicting results.[1] Overall, some beneficial effect has been observed perhaps in a subgroup of patients.[2] The general consensus of opinion is that all patients with CAL should, ideally, have a 'trial' of oral steroid. However, there are numerous side effects in the long-term use of oral corticosteroids, and such preparations are usually stopped or tapered after two weeks even in responders.

In contrast, inhaled corticosteroids are relatively safe, even with long-term use. They have been shown to be highly effective in the management of asthma, but their effect on patients with CAL is unclear. *Weir et al.*[3] found that they are less effective than oral steroids, but their patients were only treated for two weeks, which is considered insufficient.[4] The present study was designed to evaluate the effect of a longer course (eight weeks) of inhaled corticosteroids on CAL.

PATIENTS AND METHODS

Twenty patients (16 males) from the respiratory clinic of the Prince of Wales Hospital, Hong Kong, were recruited into the study. Their mean age was 66 years (range 52-75). Criteria for inclusion in the study were:

1. Chronic bronchitis and/or emphysema with forced expiratory volume in one second (FEV1) of 70% or less of predicted normal value and FEV1/ forced vital capicity (FVC) ratio of 60% or less.

2. Less than 15% increase in FEV1 after inhalation of 400 μg of salbutamol.

3. No clinical asthma (significant variability of symptoms).

4. Not on oral or inhaled corticosteroids for at least four weeks prior to entrance into the study.

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5. No acute exacerbation within the preceding four weeks.

Patients were excluded if they had unstable or uncontrolled heart failure, hypertension or coronary artery disease.

In the first out-patient attendance, a complete history was taken. Spirometry was performed with a dry bellow spirometer (Vitalograph). Skin prick tests were done with ten commercially available allergens (Bencard). A wheal of 2 mm or greater was considered positive provided that the reaction to the control solution (normal saline) was negative. A posteroanterior chest radiograph was taken. Arterial blood gas tension was measured from a sample taken from the radial artery. The inhaled and oral drugs taken by the patients were recorded. The patients were instructed on the use of the mini-Wright peak flow meter and the proper use of inhalers. A practice six minute walk[5,6] was done to familiarize the patients with the test and this result was not used in the final analysis. The patients were then instructed to perform daily measurements of peak expiratory flow rates (PEFR) and enter the readings into a diary card. They continued to take all regular prescribed drugs at the same dosage throughout the study. These were mainly inhaled salbutamol and ipratropium, although some patients also took oral β2 agonists and theophylline.

The study was initially designed to be a randomised, double-blind, placebo controlled, cross-over study similar to that of Mendella *et al.*[7] However, the randomisation was subsequently changed without notifying the chief investigators. All patients received placebo followed by budesonide treatment. Therefore, the design of the study became a double-blind, placebo controlled, cross-over study (Fig. 1). At each visit, clinical and laboratory assessment was undertaken by staffs who were unaware of the study design. To ensure clinical stability, all measurements (FEV1, FVC and PEFR) had to be within 10% at the beginning and end of the run-in period. Patients who were 'unstable' were retested two weeks later, and accepted only if the two most recent sets of measurements were within 10% of each other. Once accepted, patients were issued fresh unlabelled inhalers containing either placebo or budesonide every four weeks at the end of the run-in period. At each visit, the following were recorded:

1. Symptom score-dyspnea grade[8] (1-5) and well being (better, same or worse).

2. Lung function tests-FEV1, FVC, FEV1/FVC ratio, total lung capacity (TLC) and residual volume (RV) were measured.

3. Six minute walking distance (6MD).

4. Bronchial challenge test with histamine by the method of Yan *et al.*[9] if FEV1 was greater than 50% of predicted.

5. PEFR : the overall mean, morning mean and daily fluctuation. Daily PEFR fluctuation was calculated by the following formula:

$$\text{PEFR fluctuation on day 1} = \frac{\text{Maximum–minimum PEFR on day 1}}{\text{(morning PEFR + evening PEFR)/2}} = X_1$$

$$\text{PEFR fluctuation (day) over 1 week} = \frac{X_1 + X_2 + \ldots\ldots + X_7}{7}$$

6. Drugs used.
7. Weight of aerosol canisters to assess compliance.

RESULTS

Of the 20 patients enrolled into the study, four patients were excluded because of poor compliance, one patient because of recurrence of bladder carcinoma and one patient because of unstable lung function during the run-in period. During the study period none of the patients had an acute exacerbation of their CAL.

The baseline data of the fourteen patients entered into the study were summarised in Table 1. Only one patient had positive skin prick test and another one had sputum eosinophilia. None of the patients had peripheral blood eosinophilia. Three patients were current smokers and the rest were ex-smokers.

The results of clinical and laboratory assessment at each visit were summarised in Table 2. There was no significant change in the overall spirometric measurements and symptom score except a reduction in daily PEFR fluctuation ($p < 0.05$). However, individual patients showed significant increase in FEV1. Two patients (14%) had over 30% (49.5 and 30.3%, respectively) increase and two patients had 15-20%

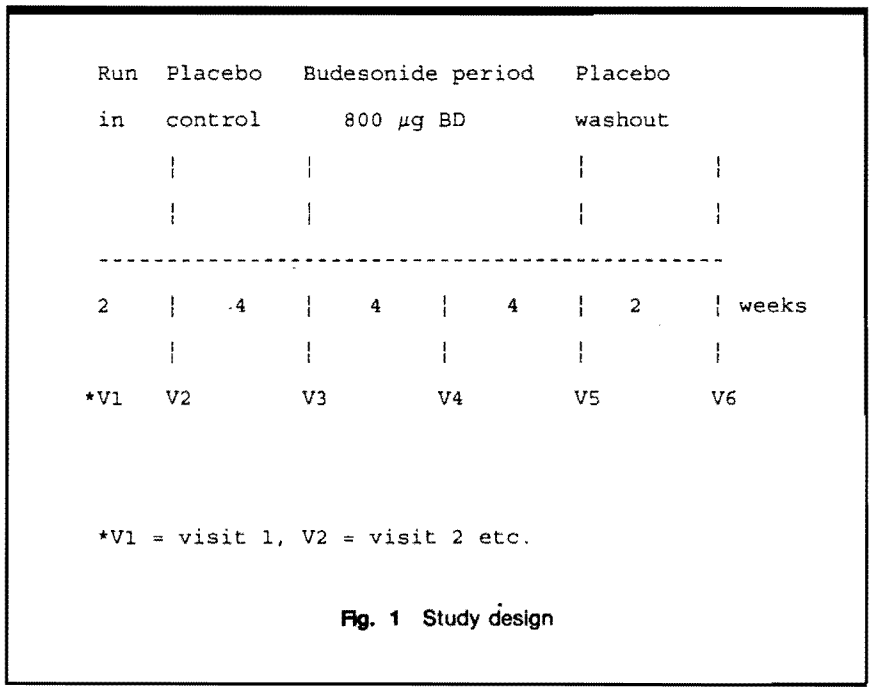

Fig. 1 Study design

Table 1. Baseline data of the 14 patients (11 M, 3 F) enrolled into the study.

Parameter	Mean ± SD
Age (years)	64.5 ±7.3
Smoking (pack/years)	39.5 ±20.3
FEV1 (L)	0.99 ±0.50
FVC (L)	2.07 ±0.58
Δ FEV1	7.2 ±6.3
PaO_2 (KPa)	9.9 ±2.3
$PaCO_2$ (KPa)	6.1 ±1.8

ΔFEV1 -- percentage increase in FEV1 after inhaling 400 μg of salbutamol.

(19.5 and 15.6%, respectively) increase in FEV1 after treatment with inhaled budesonide. The corresponding changes in FEV1 in these four patients after placebo treatment were 0, -19.5, -9.6 and -0.7%, respectively. If we only accept the criteria for a positive response to steroid as increase of FEV1 of 30% or more as suggested by Mandella *et al.*[7] then only one patient had significant improvement and one had marginal response to inhaled corticosteroids. Despite the improvement in the spirometric indices, there was no significant symptomatic improvement in these two patients. None of them had a history of allergy, positive skin test, peripheral blood or sputum eosinophilia. After placebo treatment, three of the 14 patients had a 10-15% increase and one had a 19% increase in FEV1 which were within the range of spontaneous variability of upto 30% as suggested by Mandella *et al*[7]. None of the patients experienced untoward side effects such as sore-throat or hoarseness of voice as a result of budesonide treatment.

Bronchial challenge tests could be performed in four patients only because of inadequate lung function in the rest. The cumulative dose of histamine required to produce a 20% fall in FEV1 (PD20) is shown in Table 3.

DISCUSSION

One of the earliest effects of smoking on the bronchial tree is respiratory bronchiolitis associated with clusters of pigmented alveolar macrophages.[10] The macrophages release chemotactic factors that attract neutrophils into the lungs.[11] The macrophages[12] and/or the neutrophils may be a source of elastolytic activity that leads to airway damage and emphysema. The changes in the small airways in chronic smokers have two distinct components, one potentially reversible and the other irreversible. The reversible component is related to mucus plugging and inflammation of the airways. The irreversible component is related to fibrosis, distortion, narrowing and obliteration of small airways.[13] Theoretically, patients with predominant airway inflammation may respond to corticosteroids while those with predominant fibrosis are unlikely to do so.

In clinical practice, however, steroid responsiveness in patients with CAL cannot be predicted reliably. Some studies suggested features of asthma, including an acute

Table 2. Effect of placebo and budesonide inhaler treatment on symptoms and lung function tests.

	Visit 1	Visit2	Visit 3	Visit 4	Visit 5	Visit 6
Dyspnoea grade (1-5)	3.1 ±0.7	3.1 ±0.8	3.1 ±1.0	2.5 ±0.9	2.4 ±0.9	2.6 ±1.0
Well being Better = 1 Same = 0 Worse = −1	0.0 ±0.0	0.2 ±0.0	0.07 ±0.07	0.36 ±0.38	0.36 ±0.53	0.21 ±0.54
Pulmonary function						
FEV_1 (L)	0.99 ±0.50	0.95 ±0.43	0.97 ±0.47	0.97 ±0.50	1.00 ±0.52	0.97 ±0.53
FVC (L)	2.07 ±0.58	2.08 ±0.54	2.05 ±0.51	2.10 ±0.57	2.10 ±0.55	2.10 ±0.65
TLC (L)	5.02 ±1.00	5.05 ±0.82	5.10 ±0.99	5.04 ±0.94	5.05 ±0.86	4.89 ±0.83
RV (L)	2.77± 0.81	2.72 ±0.71	2.94 ±0.73	2.72 ±0.69	2.77 ±0.64	2.64 ±0.64
6MD (metres)	370 ±48	372 ±49	353 ±76	384 ±54	373 ±62	359 ±87
PEFR (L/min)						
Overall mean	212 ±84	213 ±81	225 ±90	205 ±95	229 ±80	No data
Morning mean	204 ±80	207 ±79	219 ±89	203 ±94	227 ±81	No data
Daily fluctuation	0.19 ±0.08	0.16 ±0.09	*0.21 ±0.09	0.11 ±0.08	*0.14 ±0.09	No data

Data presented as mean ± SD.
*$P < 0.05$

Table 3. Result of histamine challenge tests in four patients.

Patient number	Visit 3	Visit 5	Washout period
4	1.20	0.85	1.10
5	2.60	5.00	1.40
10	1.95	8.00	8.00
14	0.36	0.31	0.32

increase in FEV1 after bronchodilators[7], spontaneous variability of FEV1 and blood eosinophilia are more common among responders[14] but other authors were unable to identify such associations.[2] Therefore clinicians still have to rely on a formal steroid trial.

Conventionally, a formal steroid trial consists of administering oral steroids in high doses for two weeks. However, recent studies[3,4] showed that such a duration may be insufficient. It is possible that corticosteroid for a longer period may produce improvement that is not apparent with short-term treatment but, because of the complications associated with prolonged oral steroids, most clinicians are reluctant to continue the drug for longer periods. Inhaled corticosteroid, although seemingly less effective than oral corticosteroid[3,15], is relatively free of side effects and can be used for longer term treatment. However, most of the published data involved relatively short treatment periods of up to two weeks only[3,14-16]. The studies were mostly single-blind[14,16] and relatively few were double-blind[3,15], placebo controlled study.[3]

In our present study, four patients (29%) had greater than 15% increase in FEV1 after treatment. If we only accept the criterion for a positive response to steroid as increase in FEV1 of 30% or more as suggested by Mandella

et al.[7], then only one of our patients had a significant response and another had marginal response to inhaled corticosteroids. Therefore, despite eight weeks of inhaled budesonide, only a few patients with CAL showed any sign of improvement with inhaled corticosteroid treatment. None of these two responders had features to suggest an allergic component such as a history of allergic disorders, variability of symptoms, positive skin prick test, peripheral blood or sputum eosinophilia. Because of the strict criteria for inclusion in our study, it is unlikely that patients with asthma were recruited. We postulate that the responders had significant airway inflammation which may respond to inhaled corticosteroid treatment while the others had predominant airway fibrosis and obliteration[13] that were irreversible on treatment. The improvement in FEV1 in two patients and the overall reduction in daily PEFR fluctuations suggest that inhaled corticosteroids may have marginal benefits in patients with CAL. However, since the number of responders is small and inhaled corticosteroid therapy is costly, we do not recommend giving inhaled corticosteroids to all patients with CAL. Nontheless, in patients with CAL who remain breathless despite treatment with maximum doses of bronchodilators, a trial of inhaled corticosteroids therapy may be worthwhile.[17]

Because the response to inhaled corticosteroids may be delayed[4], we administered inhaled budesonide for eight weeks to the patients in our study. A longer duration of treatment may be desirable, but then practical difficulties will increase eg with patient compliance and occurrence of acute exacerbations during the study period. Thus, four patients had to be withdrawn because of poor drug compliance. There are some preliminary data that prolonged courses of inhaled corticosteroids may be beneficial in a subgroup of patients with CAL.[18] However, this study may be criticized because the study population was clearly unusual and highly selective with an excessive yearly decline in FEV.[19] A large scale multicentre study of the long-term (3 years) effect of inhaled corticosteroids on CAL is now underway in Europe.[20] The results of this study may give as a clearer answer of the potential benefits of long-term inhaled corticosteroid in CAL.

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