Original articles

Effects of high dose inhaled beclomethasone dipropionate, 750 μg and 1500 μg twice daily, and 40 mg per day oral prednisolone on lung function, symptoms, and bronchial hyperresponsiveness in patients with non-asthmatic chronic airflow obstruction

D C Weir, P S Burge

Abstract

***Background*—The effect of treatment with inhaled corticosteroids in patients with non-asthmatic chronic airflow obstruction is still disputed. Whether any physiological improvements seen are accompanied by changes in bronchial responsiveness and symptoms and quality of life is also still unclear.**

***Methods*—A sequential placebo controlled, blinded parallel group study investigating the effect of three weeks of treatment with inhaled beclomethasone dipropionate (BDP), 750 μg or 1500 μg twice daily, and oral prednisolone, 40 mg per day, was carried out in 105 patients with severe non-asthmatic chronic airflow obstruction (mean age 66 years, mean forced expiratory volume in one second (FEV_1) 1·05 litres [40% predicted], geometric mean PD_{20} 0·52 μmol). End points assessed were FEV_1, forced vital capacity (FVC), and peak expiratory flow (PEF), bronchial responsiveness to inhaled histamine, and quality of life as measured by a formal quality of life questionnaire.**

***Results*—Both doses of BDP produced equivalent, small, but significant improvements in FEV_1 (mean 48 ml), FVC (mean 120 ml), and PEF (mean 12·4 l/min). The addition of oral prednisolone to the treatment regime in two thirds of the patients did not produce any further improvement in these parameters. Inhaled BDP produced a treatment response in individual patients (defined as an improvement in FEV_1, FVC, or mean PEF of at least 20% compared with baseline values) more commonly than placebo (34% *v* 15%). The two doses of BDP were equally effective in this respect and again no further benefit of treatment with oral prednisolone was noted. Treatment with BDP for up to six weeks did not affect bronchial responsiveness to histamine. Small but significant improvements were seen in dyspnoea during daily activities, and the feeling of mastery over the disease.**

***Conclusions*—High dose inhaled BDP is an effective treatment for patients with chronic airflow obstruction not caused by asthma. Both objective and subjective measures show improvement. Unlike asthma, no improvement in bronchial responsiveness was detected after six weeks of treatment.**

(*Thorax* 1993;**48**:309–316)

Inhaled corticosteroids are used extensively as effective maintenance treatment for patients with asthma.[1] A few studies have also investigated the role of inhaled steroids in the treatment of chronic airflow obstruction not caused by asthma. These have come to differing conclusions with some authors, including ourselves, coming to positive conclusions,[2 3] while others have found no effect of treatment with inhaled corticosteroids on lung function and symptoms in patients with chronic airflow obstruction.[4 5] Our own earlier positive study is the largest published to date, and the two negative studies may have studied insufficient patients to be certain a significant effect of inhaled corticosteroids would not be missed. Recent meta-analyses of studies investigating the effect of oral corticosteroids in patients with chronic airflow obstruction have shown that the better designed larger studies are those that tend to show a significant effect of treatment.[6]

In our previous study we showed that inhaled beclomethasone, 500 μg three times daily, was about half as effective as oral prednisolone, 40 mg per day, in improving indices of airflow obstruction over two weeks in patients with non-asthmatic chronic airflow obstruction.[3] We postulated that the difference in response rate to the inhaled and oral corticosteroid drugs may have been due simply to a dose effect and that higher doses of inhaled beclomethasone may be as effective as oral prednisolone.

Recent studies have suggested that inhaled corticosteroids improve lung function in

Chest Research Institute, East Birmingham Hospital, Birmingham B9 5ST
D C Weir
P S Burge

Reprint requests to:
Dr D C Weir, Osler Chest Unit, Churchill Hospital, Headington, Oxford OX3 7LJ

Received 13 May 1992
Returned to authors 22 July 1992
Revised reversion received 28 October 1992
Accepted 4 November 1992

asthmatic patients at least partly by suppressing airway inflammation and reducing bronchial hyperresponsiveness.[7-9] It is reasonable to suppose that they may have similar effects in patients with airway narrowing caused by smoking and other non-allergic causes where bronchial wall inflammation is also apparent.[10] Indeed, the reduction of bronchial hyperresponsiveness by inhaled corticosteroids in patients with chronic airflow obstruction may suggest that in the majority of these patients the underlying disease process may be asthmatic in nature and that all that short term "steroid trials" accomplish is to identify "missed asthmatics".[11] Three recent small studies, however, have failed to show any beneficial effect of inhaled budesonide on bronchial hyperresponsiveness at doses between 800 μg and 1600 μg per day in smokers with[5 12] and without[13] chronic airflow obstruction.

The aim of this study was to investigate the effect of two high doses of inhaled beclomethasone dipropionate (BDP) and oral prednisolone on lung function, bronchial responsiveness to inhaled histamine, and subjective parameters in patients with non-asthmatic chronic airflow obstruction.

Methods

PATIENTS

One hundred and five patients with chronic airflow obstruction not clinically caused by asthma were recruited from routine outpatient chest clinics. The inclusion criteria for entry into the study were: (a) age 18 years or over; (b) chronic airflow obstruction defined as a ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) of less than 65% and a FEV_1 of less than 70% of the predicted value; and (c) symptoms occurring only during adult life. Patients were excluded if: (a) they had a past or present clinical diagnosis of asthma; (b) they had been treated with inhaled or oral corticosteroids in the previous three months; (c) they had suffered an infective exacerbation of their disease (acute on chronic bronchitis) within the four weeks before recruitment; or (d) they had a history of poorly controlled concomitant disease—for example, diabetes mellitus, active peptic ulcer disease, uncontrolled congestive heart failure, or untreated pulmonary tuberculosis.

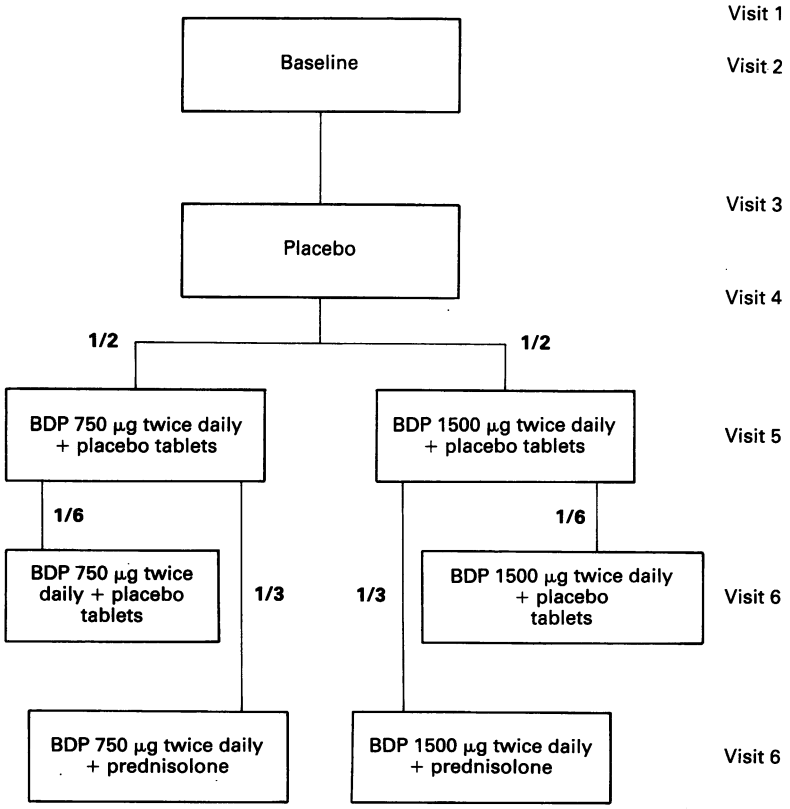
Reversibility of the airflow obstruction to bronchodilators was not included in the criteria because of the relationship between reversibility and the starting FEV_1[14] which makes the interpretation of apparent reversibility to FEV_1 in patients with low starting FEV_1 extremely difficult. A diagnosis of asthma was made at the time of the first assessment if patients had a history of variability in symptoms (except in association with infections), acute attacks of wheezing and breathlessness, or deterioration in symptoms following exposure to a specific allergen.

TRIAL DESIGN

The design of the trial was single blind with three sequential treatment periods, each of three weeks, to overcome the carry over effect of corticosteroids reported to be up to six weeks.[15] The treatment periods were preceded by a baseline period of 14–21 days during which time bronchodilator therapy was rationalised and the various baseline investigations performed. For the final seven days of the baseline period and throughout the remainder of the trial bronchodilator treatment was continued unchanged.

At the end of the baseline period the patients were randomly allocated to one of four possible treatment regimes over the ensuing nine weeks—that is, a parallel group design was used (fig). The randomisation was blind to both the investigator and the patients. The design employed a double dummy technique. For each treatment period patients were provided with two identical inhalers and tablets. Patients were instructed to take three puffs from each inhaler twice daily. Inhalers contained either placebo or BDP, 250 μg per puff. Eight tablets were prescribed each day to be taken in the morning after breakfast. Inhalers were taken via a volumatic spacer device (Allen and Hanburys, Greenford, Middlesex). Patients were instructed at each attendance on how to take inhalers with this device. In addition both written and verbal instructions were given to each patient at each attendance on the dose of each medication to be taken.

In all patients the first treatment period



Schematic representation of the trial design. Each phase of the trial was 3 weeks long, with assessments on the final day of each treatment phase. The proportion of patients following each pathway is shown in bold type.

consisted of placebo inhalers and tablets for three weeks. For the second treatment period the patients received either inhaled BDP 750 μg twice daily (one active inhaler) plus placebo tablets, or inhaled BDP 1500 μg twice daily (two active inhalers) plus placebo tablets. For the final treatment phase, the inhaled therapy allocated during the second treatment phase was continued unchanged but two thirds of the patients also received oral prednisolone, 40 mg per day, the remaining one third continuing with placebo tablets.

The patients attended the laboratory on three occasions during the baseline period for pretreatment assessments to be made—that is, day −21 (start of baseline), day −7 (midway through baseline period), and day 0 (start of the placebo treatment). They were then assessed on the final day of each treatment period.

Cannisters of inhaled drug were weighed after each visit and returned tablets counted without the patient's knowledge to assess compliance. The protocol was approved by the hospital ethics committee and written informed consent was obtained from all patients.

MEASUREMENTS

Lung function

Patients were instructed to refrain from inhaled bronchodilators for six hours and oral bronchodilators for 24 hours before clinic visits. All lung function measurements were performed at the same time of day after 20 minutes rest.

FEV_1 and FVC were measured on a dry wedge spirometer (Vitalograph). The highest value of at least three attempts was recorded and used for future analysis, providing the highest two readings of FEV_1 were within 50 ml or 5% of each other. For subsequent analysis the baseline FEV_1 and FVC were taken as the mean of the measurements recorded on the three baseline visits before any treatment.

Reversibility of FEV_1 and FVC to 200 μg salbutamol and 72 μg ipratroprium bromide was measured on separate days during the baseline period. The drug was administered by a Volumatic spacer device (Allen and Hanburys, Greenford, Middlesex) by the investigator and the response measured 20 minutes later. Reversibility to FEV_1 was expressed as a percentage of the predicted FEV_1:

$$\frac{\text{postbronchodilator } FEV_1 - \text{prebronchodilator } FEV_1}{\text{predicted } FEV_1} \times 100\%$$

Bronchial responsiveness to inhaled histamine was measured by the method of Yan *et al*[16] on the second of the baseline visits and after each treatment phase in all patients with an FEV_1 greater than 0·75 litres. The cumulative dose of histamine which produced a 20% fall in the FEV_1 (PD_{20}) was estimated by linear interpolation of a log dose-response plot, with extrapolation to one doubling dose above the maximum administered.

During the baseline period patients also had carbon monoxide gas transfer measured by the single breath technique using a Morgan transfer test module and static lung volumes were measured by a closed circuit helium dilution technique. Measurements of total white cell count, eosinophil count, serum IgE level, and serum thiocyanate were carried out in all patients. Exhaled carbon monoxide concentration was measured with a portable analyser (Ecocheck EC50; PK Morgan, Chatham, Kent). An exhaled carbon monoxide concentration above 8 ppm or a serum thiocyanate concentration greater than 70 μmol/l were considered as evidence of current cigarette consumption and classified patients as current smokers irrespective of their claimed smoking habit. Skin test reactivity to *Dermatophagoides pteronyssinus*, *Aspergillus fumigatus*, cat fur, dog hair, grass pollens, *Cladosporium* spp, and *Penicillium* was measured in all patients. A positive test was considered to be a weal of 3 mm diameter greater than that seen to the diluent control.

Diary cards

Throughout the study patients were asked to record peak expiratory flow (PEF) and a breathlessness score on a diary card. Patients were provided with a new mini Wright peak flow meter and asked to record the PEF four hourly starting immediately on rising. They were instructed to make three readings and to record the highest of the three readings provided the two top readings were within 20 l/min of each other. If this criterion was not met they were asked to take further readings until it could be fulfilled. At the end of each day patients were asked to record their breathlessness over the previous 24 hours on a seven point open ended scale. The lowest value of the scale (1) was chosen to represent a state of no breathlessness whereas the maximum score (7) was described as the worst breathlessness the patient had ever experienced.

Quality of life questionnaire

On the final baseline visit and after each of the treatment phases the patients answered a doctor administered quality of life questionnaire.[17] The questionnaire consisted of five individualised questions about episodes of dyspnoea experienced by the patient during everyday activities. A further 15 questions covered three further broad areas of the patient's life, mastery over the disease, emotional function, and fatigue. In patients not identifying five activities consistently causing breathlessness, the dyspnoea score was standardised by dividing the total score by the number of dyspnoea questions answered and multiplying the result by five.

Oxygen cost diagram

On two occasions during the baseline period and at the end of each treatment phase patients were asked to complete a modified oxygen cost diagram.[18] The patient was instructed to "mark the line at a point above which you would become breathless".

DATA HANDLING AND STATISTICAL ANALYSIS

The subjective data recorded on diary cards were averaged over the final seven days of each phase and the mean used for subsequent analysis. Peak flow readings were analysed daily, calculating the mean and diurnal variation as amplitude expressed as a percentage of the mean daily PEF:

$$\text{Daily diurnal variation in PEF} = \frac{\text{daily maximum PEF} - \text{daily minimum PEF}}{\text{daily mean PEF}} \times 100\%$$

The calculated daily values were averaged over the final seven days of each treatment period to give the values used in the subsequent analysis. PD_{20} and serum IgE data were log transformed before analysis. Comparisons of the baseline characteristics of the parallel treatment groups were performed by unpaired Student's t tests for normally distributed continuous data, Mann-Whitney U test for non-parametric continuous data, and χ^2 test for categorical data.

To compare the efficacy of placebo, inhaled BDP, and oral prednisolone on lung function, the FEV_1 and FVC recorded on the final day of each treatment phase, and the mean PEF recorded over the last seven days of the treatment phase, were selected as end points. The response to treatment in these physiological variables after placebo and inhaled BDP was assessed by a repeated measures analysis of variance. For analysis of the data after the final phase of active treatment, when two thirds of the patients received oral prednisolone in addition to inhaled BDP, the change in each variable from the previous phase was calculated. The change was compared between the two prednisolone treatment groups by an unpaired Student's t test, combining the inhaled BDP dose groups.

In addition a "categorical analysis" was undertaken after classifying each patient as a treatment responder or non-responder for each of the three treatment phases. Response to treatment was defined as an improvement in prebronchodilator FEV_1, or FVC recorded on the final day of each treatment phase, or mean PEF over the last seven days of the treatment phase of at least 20% when compared with the baseline value. The difference in response rates to placebo and inhaled BDP was assessed by McNemar's test. The response rate after the final treatment phase was compared by a χ^2 test for the two final phase treatment groups, again combining the BDP dose groups.

The effect of treatment on bronchial responsiveness to inhaled histamine and on subjective parameters was assessed by analysis of variance as above. Predicted lung function values were derived from the published equations of the European Community for Coal and Steel.[19]

Table 1 Characteristics of the two BDP dosage groups expressed as mean (SE) unless indicated.

	Dose group	
	BDP 750 μg twice daily (n = 47)	*BDP 1500 μg twice daily (n = 51)*
Females (number)	15	14
Age (years)	66 (1·0)	65 (1·0)
FEV_1 (litres)	1·07 (0·07)	1·05 (0·07)
FEV_1/FVC (%)	41·2 (1·8)	37·8 (1·7)
Mean PEF (l/min)	231 (12)	236 (13)
TLCO (% predicted)	70·3 (3·8)	67·4 (3·8)
KCO (% predicted)	61·4 (3·4)	56·4 (3·2)
Diurnal variation in PEF (% predicted)	10·4 (0·8)	11·0 (0·9)
FEV_1 reversibility to 200 μg salbutamol (% predicted)	6·4 (0·6)	5·6 (0·9)
FEV_1 reversibility to 80 μg ipratropium bromide (% predicted)	4·9 (0·7)	4·8 (0·9)
Serum IgE (kU/l) (geometric mean)	83	64
Number with positive skin tests	10	10
Current smokers	17	28
Ex-smokers	29	23
Never smokers	1	0
Cigarette consumption (pack years)	51 (5·0)	46 (4·1)

BDP—beclomethasone dipropionate; FEV_1—forced expiratory volume in one second; FVC—forced vital capacity; PEF—peak expiratory flow; TLCO—carbon monoxide transfer factor; KCO—carbon monoxide transfer coefficient.

Results

One hundred and twelve patients entered the baseline period of the study. Three patients were unable to complete the diary card or follow the protocol, and four experienced an infective exacerbation of their disease requiring treatment with antibiotics and oral corticosteroids, leaving 105 patients (75 men) who were randomised to receive treatment.

The mean age of the patients studied was 66 (range 49–78) years. One hundred and four subjects either had been (n = 57) or were (n = 47) smokers, with a mean (SE) cigarette consumption of 49 (3·1) pack years. Twenty three patients exhibited skin test reactivity to the allergens used, and the geometric mean (range) IgE level was 75 (25–4810) kU/l. The mean (SE) FEV_1 was 1·05 (0·05) litres, or 40 (1·5)% of the predicted value, with a mean (SE) FEV_1 to FVC ratio of 39 (1·2)%. The mean carbon monoxide gas transfer coefficient (KCO) was reduced at 1·03 (0·04) mmol/kPa/min/l, or 58 (2·3)% predicted. The mean (SE) FEV_1 reversibility to salbutamol was 144 (13) ml, or 5·7 (0·5)% as a percentage of the predicted FEV_1. The geometric mean PD_{20} was 0·52 (range 0·04–16) μmol histamine.

Withdrawals

Fifty three patients were randomised to receive 750 μg twice daily BDP and 52 to receive 1500 μg twice daily. During the placebo phase six patients were withdrawn from the lower dose group: three suffered infective exacerbations of their disease, one failed to return, one developed abnormal liver function, and one was unable to tolerate the pressurised inhalers due to wheezing and cough. One patient was withdrawn at this stage from the higher dose group due to an infective exacerbation. All patients completed the inhaled BDP treatment phase, 47 receiving 750 μg twice daily and 51 receiving twice

Table 2 Mean (SE) values for FEV_1, FVC, and PEF at baseline, after placebo and inhaled BDP

	BDP dose (twice daily)	Baseline	After placebo	After BDP
FEV_1(litres)	750 μg	1·07 (0·07)	1·07 (0·07)	1·11 (0·07)
	1500 μg	1·05 (0·07)	1·01 (0·07)	1·10 (0·07)
Treatment effect: $F = 11·14$; df = 2, 192; $p < 0·0001$.				
Interaction: $F = 1·35$; df = 2, 192; NS.				
FVC (litres)	750 μg	2·58 (0·11)	2·58 (0·10)	2·68 (0·11)
	1500 μg	2·76 (0·12)	2·78 (0·12)	2·90 (0·11)
Treatment effect: $F = 8·63$, df = 2, 192; $p < 0·0005$.				
Interaction: $F = 0·14$, df = 2, 192; NS.				
Mean PEF (1/min)	750 μg	231 (12·6)	235 (13·0)	243 (13·6)
	1500 μg	237 (14·0)	235 (14·4)	250 (14·9)
Treatment effect: $F = 16·5$; df = 2, 188; $p < 0·0001$.				
Interaction: $F = 1·14$; df = 2, 188; NS.				

BDP—beclomethasone dipropionate; FEV_1—forced expiratory volume in one second; FVC—forced vital capcity; PEF—peak expiratory flow.

Table 3 Response to inhaled BDP and placebo in individual patients.

	BDP group	
Placebo group	Responder	Non-responder
Responder	11	4
Non-responder	22	61

BDP—beclomethasone dipropionate.

daily 1500 μg. During the second active treatment phase four patients were withdrawn in the combined treatment group. One attributed alopecia to the treatment, one patient developed an unrelated pneumothorax, a further patient suffered an infective exacerbation, and the final patient developed symptomatic hyperglycaemia. Two patients in the group continuing on inhaled BDP alone were withdrawn, one because of severe depression necessitating inpatient treatment, the other because of an infective exacerbation.

Fewer than 15% of the patients were considered to be poorly compliant with therapy as judged by cannister weighing and counting of returned tablets.

Table 4 Mean (SE) scores for the dimensions of the quality of life questionnaire, diary card breathlessness scores, and oxygen cost diagram at baseline, and after treatment with placebo and inhaled BDP.

	BDP dose (twice daily)	Baseline	After placebo	After BDP
Dyspnoea	750 μg	18·0 (0·8)	19·0 (0·9)	20·4 (1·0)
	1500 μg	17·7 (0·7)	19·4 (0·9)	21·3 (1·0)
Treatment effect: $F = 24·96$; df = 2, 91; $p < 0·0001$.				
Interaction: $F = 0·92$; df = 2, 91; NS.				
Fatigue	750 μg	17·6 (0·7)	17·8 (0·7)	18·8 (0·8)
	1500 μg	17·4 (0·8)	16·9 (0·7)	17·3 (0·8)
Treatment effect: $F = 3·61$; df = 2, 94; $p < 0·03$.				
Interaction: $F = 2·76$; df = 2, 94; NS.				
Emotional function	750 μg	33·4 (1·2)	35·1 (1·2)	36·6 (1·2)
	1500 μg	32·8 (1·3)	33·1 (1·3)	32·9 (1·5)
Treatment effect: $F = 4·89$; df = 2, 94; $p < 0·01$.				
Interaction: $F = 4·2$; df = 2, 94; $p < 0·02$.				
Mastery	750 μg	19·7 (0·9)	20·1 (0·8)	20·3 (0·9)
	1500 μg	20·0 (0·8)	20·9 (0·8)	21·8 (0·8)
Treatment effect: $F = 9·25$; df = 2, 94; $p < 0·0001$.				
Interaction: $F = 2·75$; df = 2, 94; NS.				
O_2 cost	750 μg	121 (5·5)	127 (6·2)	124 (5·5)
	1500 μg	118 (5·4)	124 (5·4)	130 (5·8)
Treatment effect: $F = 5·8$; df = 2, 89; $p < 0·005$.				
Interaction: $F = 2·34$; df = 2, 89; NS.				
Breathlessness score	750 μg	3·1 (0·2)	3·2 (0·2)	2·9 (0·2)
	1500 μg	2·8 (0·2)	3·0 (0·2)	2·6 (0·2)
Treatment effect: $F = 9·52$; df = 2, 88; $p < 0·00002$.				
Interaction: $F = 0·31$; df = 2, 88; NS.				

EFFECT OF INHALED BDP

Spirometry and mean PEF

No significant differences in the baseline characteristics of the two BDP dosage groups were detected (table 1). A small but significant effect of inhaled BDP on all three physiological measures was seen (table 2). There was no significant difference between the two doses of BDP, and no dose-treatment interaction was detected for any of the three end points used. For the combined BDP dose groups the mean improvement from the baseline value after active treatment was 48 ml for FEV_1, 120 ml for FVC, and 12·4 l/min for mean PEF.

Response to inhaled BDP in individual patients

To assess response to treatment in individual patients the response rate to the two doses of inhaled BDP was compared initially. In the patients receiving a twice daily dose of 750 μg, 16 of 47 (34%) showed a response as defined above; in the 1500 μg group 17 of 51 (33%) responded ($\chi^2 = 0·06$, NS). In the responders the response was seen in one parameter in 27 patients (FEV_1, 12; FVC, 7; PEF, 8), in two parameters in four (FEV_1 + PEF, 1; FEV_1 + FVC, 3), and in all three end points in two patients.

To assess the efficacy of inhaled BDP against placebo both BDP dose groups were combined. In individual patients a response occurred in 15 patients (15%) receiving placebo, and in 33 patients (34%) receiving inhaled BDP (table 3). This difference in response rates was significant ($p < 0·001$).

PD_{20} histamine

In the 66 patients in whom the PD_{20} was measured at baseline and after placebo treatment the 95% range for the repeatability of a single estimation of PD_{20} was 1·99 doubling concentrations. Treatment with inhaled BDP at either dose for three weeks had no significant effect. The geometric mean baseline PD_{20} in the group receiving 750 μg twice daily was 0·56 μmol; after placebo it was 0·49 μmol, and after BDP 0·61 μmol. In the group receiving 1500 μg twice daily the baseline PD_{20} was 0·65 μmol; after placebo it was 0·51 μmol and after BDP 0·58 μmol.

In the one third of patients continuing on inhaled BDP alone for the final treatment phase the mean (95% CI) change in PD_{20} over this final phase was −0·41 (−0·48–1·09) doubling doses of histamine which was not significant.

Subjective measures

The subjective measures analysed were the four dimensions of the quality of life questionnaire, the diary card breathlessness scores, and the oxygen cost diagram.

Table 5 Baseline characteristics of the two final treatment phase groups expressed as mean (SE) unless indicated.

	Treatment group	
	BDP alone (n = 31)	*Prednisolone + BDP (n = 61)*
Females (number)	5	20
Age (years)	66 (1·2)	66 (0·8)
FEV_1 (litres)	1·05 (0·06)	1·08 (0·08)
FEV_1/FVC (%)	39·0 (2·2)	39·4 (1·6)
Mean PEF (1/min)	248 (17)	230 (12)
TLCO (% predicted)	67·2 (5·5)	69·4 (3·2)
KCO (% predicted)	57·2 (4·8)	59·3 (2·7)
Diurnal variation in PEF (% predicted)	9·9 (1·0)	11·5 (0·8)
FEV_1 reversibility to 200 μg salbutamol (% predicted)	5·6 (1·0)	5·8 (0·7)
Serum IgE (kU/1) (geometric mean)	54	86*
Number with positive skin test	7	11
Current smokers	15	26
Ex-smokers	16	34
Never smokers	0	1
Cigarette consumption (pack years)	49 (4·7)	47 (4·4)

* $p < 0·05$, all other comparisons non-significant. For definition of abbreviations see table 1.

A small but significant improvement in the dyspnoea score from the quality of life questionnaire was seen after treatment with inhaled BDP. No difference between the two doses given was detected. Placebo therapy also improved this measure significantly over the baseline score, but treatment with inhaled BDP caused a further small but significant increase (table 4). The three non-respiratory components of the quality of life questionnaire showed variable changes. Only the "mastery" questions showed a significant improvement after inhaled BDP compared with both placebo and baseline answers. The results of the oxygen cost diagram showed a significant improvement over baseline with both placebo and inhaled BDP, but no difference was apparent between the active drug and placebo therapy. Diary card breathlessness scores fell (improved) with inhaled BDP, but showed a small rise after placebo. Both doses of inhaled BDP were equally effective at improving this measure (table 4).

Table 6 Mean (95% confidence interval) changes in each of the lung function and subjective measures over the third treatment phase.

	BDP alone (n = 31)	*Prednisolone (40 mg) + BDP (n = 61)*
FEV_1 (ml)	26 (−69–18)	19 (−59–20)
FVC (ml)	−98 (−208–11)	−5 (−94–84)
Mean PEF (1/min)	2·8 (−6–11·6)	3·1 (−1·6–7·8)
Dyspnoea	1·7 (0·9–2·9)	0·7 (−0·1–1·5)
Fatigue	1·1 (0·05–2·2)	0·5 (−0·4–1·4)
Emotional function	1·7 (−0·08–3·5)	0·4 (−0·9–1·6)
Mastery	1·1 (0·4–1·7)	−0·1* (−0·7–0·5)
O_2 cost	4·9 (−5·1–14·9)	2·3 (−3·8–8·5)
Breathlessness score	−0·1 (−0·4–0·2)	0·1 (−0·05–0·3)

* $p < 0·05$. For definition of abbreviations see table 1.

The small improvement in the quality of life questionnaire dyspnoea score was seen in both responders and non-responders to BDP. Only responders showed improvements in the other three areas of the questionnaire, however, and in diary card breathlessness scores. The correlation between change in the dyspnoea and fatigue elements of the quality of life questionnaire (Guyatt's physical function score) and the spirometric measures was poor (Pearson correlation coefficients FEV_1, $r = 0·16$; FVC, $r = 0·14$; PEF, $r = 0·19$).

EFFECT OF ORAL PREDNISOLONE

The characteristics of the patients who received oral prednisolone, 40 mg per day, for the final treatment phase, and the smaller number who continued on inhaled BDP are given in table 5. The two treatment groups were well matched in terms of most of the likely confounding factors. The patients receiving oral prednisolone showed a higher mean serum IgE level but similar levels of skin test reactivity.

There was no significant difference between the two groups in the change in FEV_1 or mean PEF from that recorded at the end of the second (inhaled BDP) treatment phase. Neither group showed any significant change over the final treatment period in FEV_1, FVC, or mean PEF.

The categorical analysis showed that after the final treatment phase the response rate was similar in the two treatment groups. Of the patients receiving combined therapy, 19 (31%) showed a response to treatment (compared with baseline values), while 10 (32%) of the group receiving inhaled BDP alone showed a response as defined ($\chi^2 = 0·01$; df = 1; NS).

After a further three weeks of treatment with oral prednisolone and inhaled BDP there was no significant change in bronchial responsiveness. In the combined treatment group the mean (95% CI) change in PD_{20} from the value recorded after three weeks of treatment with inhaled BDP alone was 0·06 (−0·4–0·53) doubling concentrations.

The change in the dyspnoea, fatigue, and emotional function elements of the quality of life questionnaire from that recorded at the end of the second treatment phase was not significantly different in the patients receiving oral prednisolone during the third treatment phase and those patients continuing on inhaled BDP alone (table 6). The latter group showed larger mean changes in the three areas of the quality of life questionnaire, but the mastery dimension was the only component in which the differences between the final phase treatment groups were significant. The changes in the oxygen cost diagram and diary card breathlessness scores were also similar between the two third phase treatment groups.

Discussion

Our results have shown a small but significant effect of treatment for three weeks with inhaled BDP on the lung function parameters analysed. All three end points showed significant improvements, with the two doses of BDP used being equivalent in this respect. The "categorical" analysis confirms these findings. More patients showed a treatment response to predefined criteria after inhaled BDP than after placebo. Again both doses of BDP were equivalent. The addition of oral prednisolone for a further three weeks to the treatment regime did not produce any additional improvement to that seen by continuing on inhaled BDP alone.

The effect of treatment with inhaled corticosteroids on subjective measures was more variable and significant placebo effects were seen in some of the quality of life dimensions. Two of the three measures of dyspnoea used, however, showed significant improvements after treatment with BDP; the third (the oxygen cost diagram) was poorly understood by the patients studied and the results of this may therefore be unreliable. In addition the "mastery" element of the quality of life questionnaire showed significant improvements after three weeks of treatment with inhaled BDP. Again when prednisolone was added to the inhaled treatment no additional effect was noted.

We were unable to detect an effect of either three or six weeks of treatment with inhaled BDP on bronchial hyperresponsiveness to inhaled histamine in this group of patients, or any effect of combined treatment for three weeks.

Patients acted as their own controls in this study, although not in a crossover design. The sequential design chosen to limit the study group size, however, may not eliminate learning effects as an explanation for any changes seen. With the measures of airflow this can be discounted as no placebo effect was seen. Some or all of the small subjective response seen could be due to a learning effect. The observation that only responders showed significant changes in all elements of the quality of life questionnaire suggests strongly, however, that the treatment effect is significant.

The absolute mean changes in the three physiological end points after inhaled BDP were small. This reflects the large number of individuals who showed no response to treatment and the use of three criteria to define response. The mean improvement in FEV_1 after inhaled BDP is comparable with that seen after oral prednisolone in similar patients in two previous trials,[20 21] although only one third of that seen in two further studies.[22 23] The response rate in individual patients to inhaled BDP is slightly higher than that seen in our previous study,[3] and in the current study BDP was as effective as oral prednisolone. The use of a spacer device to deliver the inhaled drug and the increased intrapulmonary deposition of the drug may explain these apparently different results. The absence of a BDP dose effect may also simply reflect the plateau of the dose-response curve when a spacer device is used for drug delivery.

This is the first study investigating the effects of corticosteroids in chronic airflow obstruction that has used a formal quality of life measure to assess symptomatic benefit. The quality of life questionnaire developed by Guyatt has been used in therapeutic trials before and appears to be sensitive and responsive. In a small study comparing inhaled salbutamol and oral theophylline, Guyatt's group found significant improvements in the physical function dimension of the questionnaire, the combined dyspnoea and fatigue scores averaging 4–5.[24] The mean improvement in this score in our study was 3·6, comparable to the effects of bronchodilators. Despite quite small improvements in lung function, we, like Guyatt, also detected a significant improvement in the "mastery" scores. It is possible that a longer period of treatment would produce greater changes in quality of life in our patients, as many of the factors relating to impaired quality of life will only be indirectly related to airflow obstruction—for example, exercise limitation due to breathlessness causing disuse atrophy of limb muscles—and improvement in these factors would be expected to lag behind that in lung function. On an individual patient basis, significantly more patients showed an improvement in the physical function score of 4 or more (considered by Guyatt to be a clinically significant change) after BDP than after placebo, confirming the beneficial effect of active treatment on quality of life.

The lack of an effect of either inhaled BDP or oral prednisolone on bronchial hyperresponsiveness to inhaled histamine is in keeping with other studies.[5 12 13] Bronchial responsiveness in this group of patients with severe chronic airflow obstruction may be primarily dependent upon the geometric effects of airway narrowing, rather than reflecting airway inflammation as in asthma. Treatment with inhaled BDP was given for a maximum of six weeks and, although it is possible that a longer period of treatment may have been effective, in patients with asthma improvements in bronchial hyperresponsiveness with inhaled corticosteroids are apparent, although not maximal, after a similar period of treatment.

A further possible criticism of this study is the patient selection criteria used. The criteria adopted were clinically based as we were keen to study the patients in whom a "trial of steroids" is recommended.[11] Only one patient was not or had not been a cigarette smoker, the majority showed little reversibility of FEV_1 to bronchodilators, and there was a substantial irreversible element to the airflow obstruction in most patients. A large degree of reversibility in FEV_1 and a return of the airways obstruction to normal or near normal values either spontaneously or after a bronchodilator appear to be the major factors governing diagnostic labelling of patients with

chronic airflow obstruction.[25] Using these criteria most of the patients recruited to our study would not be labelled asthmatic. Until better methods of distinguishing between asthma and non-asthmatic chronic airflow obstruction become available, perhaps on the basis of basement membrane thickening in bronchial biopsies,[26] inexact clinical criteria are all that is available. The patients included in this study have similar characteristics to those in other studies described as having "smoking related chronic airflow obstruction",[27 28] and the diurnal variation in PEF was similar to that seen in the normal population.[29] We believe our results are applicable to this clinically defined and recognisable population.

Our results do not answer the question of the long term role of treatment with inhaled corticosteroids in patients with chronic airflow obstruction, and the significance of a positive "steroid trial". Why some patients are apparently unresponsive to such treatment over the short term is not clear. Only studies which attempt to characterise patients on the basis of airway disease and inflammation are likely to answer these questions comprehensively.

This study was generously supported by Glaxo Group Research Ltd. The help of the staff of the lung function laboratories at East Birmingham Hospital, the Birmingham Chest Clinic, and Solihull Hospital is gratefully acknowledged.

1 Ebden P, Jenkins A, Houston G, Davies BH. Comparison of two high dose corticosteroid aerosol treatments, beclomethasone dipropionate (1500 μg/day) and budesonide (1600 μg/day), for chronic asthma. *Thorax* 1986; **41**:869–74.
2 Wardman AG, Simpson FG, Knox AJ, Page RL, Cooke NJ. The use of high dose inhaled beclomethasone dipropionate as a means of assessing steroid responsiveness in obstructive airways disease. *Br J Dis Chest* 1988;**82**: 168–71.
3 Weir DC, Gove RI, Robertson AS, Burge PS. Corticosteroid trials in non-asthmatic chronic airflow obstruction: a comparison of oral prednisolone and inhaled beclomethasone dipropionate. *Thorax* 1990;**45**:112–17.
4 Harding SM, Freeman S. A comparison of oral and inhaled steroids in patients with chronic airways obstruction: features determining response. *Thorax* 1978;**33**:214–18.
5 Auffarth B, Postma DS, De Monchy JGR, van der Mark Th W, Boorsma M, Koeter GH. Effects of inhaled budesonide on spirometric values, reversibility, airway responsiveness, and cough threshold in smokers with chronic obstructive lung disease. *Thorax* 1991;**46**:372–7.
6 Stoller JK, Gerbarg ZB, Feinstein AR. Corticosteroids in stable chronic obstructive pulmonary disease. *J Gen Intern Med* 1987;**2**:29–35.
7 Adelroth E, Rosenhall L, Johansson S, Linden M, Venge P. Inflammatory cells and eosinophilic activity in asthmatics investigated by bronchoalveolar lavage. The effects of antiasthmatic treatment with budesonide or terbutaline. *Am Rev Respir Dis* 1990;**142**:91–9.
8 Kerrebijn KF, van Essen-Zandvliet EEM, Neijens HJ. Effect of long-term treatment with inhaled corticosteroids and beta-agonists on the bronchial responsiveness in children with asthma. *J Allergy Clin Immunol* 1987;**79**:653–9.
9 Kraan J, Koeter GH, Van der Mark ThW, Sluiter HJ, De Vries K. Changes in bronchial hyperreactivity induced by four weeks treatment with anti-asthmatic drugs in patients with allergic asthma: a comparison between budesonide and terbutaline. *J Allergy Clin Immunol* 1985;**76**:628–36.
10 Glynn AA, Michaels L. Bronchial biopsy in chronic bronchitis and asthma. *Thorax* 1960;**15**:142–53.
11 Rudd R. Corticosteroids in chronic bronchitis. *BMJ* 1984;**288**:1553–4.
12 Watson JA, Lim TK, Joyce H, Pride NB. Failure of inhaled corticosteroids to modify bronchoconstrictor or bronchodilator responsiveness in middle aged smokers with mild airflow obstruction. *Chest* 1992;**101**:350–5.
13 Engel T, Heinig JH, Madsen O, Hansen M, Weeke ER. A trial of inhaled budesonide on airway responsiveness in smokers with chronic bronchitis. *Eur Respir J* 1989;**2**: 935–9.
14 Weir DC, Burge PS. Measures of reversibility in response to bronchodilators in chronic airflow obstruction: relation to airway calibre. *Thorax* 1991;**46**:43–5.
15 Weir DC, Robertson AS, Gove RI, Burge PS. Time course of response to oral and inhaled corticosteroids in non-asthmatic chronic airflow obstruction. *Thorax* 1990;**45**:118–21.
16 Yan K, Salome CM, Woolcock AJ. Rapid method for measurement of bronchial responsiveness. *Thorax* 1983;**38**:760–5.
17 Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;**42**:773–8.
18 McGavin CR, Artvinli M, Naoe H, McHardy GJR. Dyspnoea, disability, and distance walked: comparison of estimates of exercise performance in respiratory disease. *BMJ* 1978;ii:241–3.
19 Quanjer Ph H, ed. Standardised lung function testing. *Bull Eur Physiopathol Respir* 1983;**19**(Suppl 5):1–95.
20 Evans JA, Morrison IM, Saunders KB. A controlled trial of prednisone, in low dosage, in patients with chronic airways obstruction. *Thorax* 1974;**29**:401–6.
21 Hurford JV, Little GM, Loudon HWG. The use of prednisolone in chronic bronchitis. *Br J Dis Chest* 1963; 57:133–9.
22 Shim C, Stover DE, Williams MH. Response to corticosteroids in chronic bronchitis. *J Allergy Clin Immunol* 1978;**62**:363–7.
23 Lam WK, So SY, Yu DYC. Response to oral corticosteroids in chronic airflow obstruction. *Br J Dis Chest* 1983;77:189–98.
24 Guyatt GH, Townsend M, Pugsley SO, Keller JA, Short HD, Taylor DW, *et al.* Bronchodilators in chronic airflow limitation. Effects on airway function, exercise capacity, and quality of life. *Am Rev Respir Dis* 1987; **135**:1069–74.
25 Pride NB, Vermiere PA, Allegra L. Diagnostic labels in chronic airflow obstruction: responses to a questionnaire with model case histories in North America and Western European countries. *Eur Respir J* 1989;**2**:702–9.
26 Ollerenshaw SL, Woolcock AJ. Characteristics of the inflammation in biopsies from large airways of subjects with asthma and subjects with chronic airflow limitation. *Am Rev Respir Dis* 1992;**145**:922–7.
27 Anthonisen NR, Wright EC, Hodgkin JE and the IPPB trial group. Prognosis in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986;**133**:14–20.
28 Eliasson O, De Graf AC. The use of criteria for reversibility and obstruction to define patients groups for bronchodilator trials: influence of clinical diagnosis, spirometric and anthropometric variables. *Am Rev Respir Dis* 1985;**132**:858–64.
29 Quakenboss JJ, Lebowitz MD, Kryzyzanowski M. The normal range of diurnal change in peak expiratory flow rates. Relationship to symptoms and respiratory disease. *Am Rev Respir Dis* 1991;**143**:323–30.