

Comparison of inhaled beclomethasone dipropionate 1000 µg twice daily and oral prednisone 10 mg once daily in asthmatic patients

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Abstract

Background - Glucocorticosteroids are widely used as drugs of first choice in the treatment of moderate to severe asthma. The effects of inhaled steroids in high doses have been compared with oral prednisone in asthmatic patients in a double blind crossover study.

Methods - The trial consisted of a two week run in period followed by two four week treatment periods separated by a four week washout. During the treatment period patients took either 1000 µg beclomethasone dipropionate twice daily and placebo tablets once daily, or 10 mg prednisone daily in one morning dose and placebo inhaler twice daily. The effects of treatment on the provocative dose of histamine producing a 20% fall in FEV₁ (PC₂₀ histamine), peak flow measurements at home, and spirometric measurements in the clinic, as well as on the basal and stimulated plasma cortisol levels were measured.

Results - Seventeen patients with asthma completed the study. After four weeks of treatment beclomethasone dipropionate showed a significantly better effect on morning peak expiratory flow rate than prednisone. There was a trend to a greater improvement in the PC₂₀ histamine in patients receiving beclomethasone dipropionate than in those receiving prednisone. There were no significant differences in spirometric values, symptom scores, or basal and stimulated cortisol levels between the treatments. The within treatment analysis showed a significant effect of prednisone on stimulated cortisol levels but not of beclomethasone dipropionate.

Conclusions - Beclomethasone dipropionate 1000 µg twice daily has a slightly greater therapeutic effect in this population of asthmatic patients than 10 mg of prednisone once a day with less effect on adrenocortical function.

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A major feature of bronchial asthma is an increased bronchial responsiveness to non-specific stimuli such as cold air, smoke, exercise, and pharmacological agents such as histamine and methacholine. A decrease in

bronchial hyperresponsiveness is thought to be beneficial in the treatment of asthma. Glucocorticosteroids have been shown to reduce bronchial hyperresponsiveness in a number of studies.¹⁻³

In allergic patients the late phase bronchoconstrictor response to allergen exposure has been shown to be associated with an increase of bronchial hyperresponsiveness which can be prevented by glucocorticosteroids.⁴ In non-allergic patients glucocorticosteroids may reduce bronchial hyperresponsiveness by their anti-inflammatory activity.⁵

The introduction of the topical glucocorticosteroids beclomethasone dipropionate and budesonide has provided physicians with a valuable tool for long term treatment of asthma. There are conflicting data about the relative antiasthmatic to systemic activity of oral and topical glucocorticosteroids.^{6,7} The aim of this study was to compare the effect of inhaled beclomethasone, 2000 µg daily, and oral prednisone, 10 mg daily, in diminishing bronchial hyperresponsiveness as measured by the histamine provocation test. A second objective was to compare their effects on plasma cortisol levels, lung function, and symptom scores.

Methods

SUBJECTS

Seventeen patients with asthma as defined by the ATS criteria⁸ were recruited from our outpatient department. Patient characteristics are presented in table 1. For inclusion in the study patients had to show a reversibility of at least 15% of their baseline forced expiratory volume in one second (FEV₁) following inhalation of a salbutamol nebuliser solution of 5 mg/ml for one minute. If this criterion was not met, their peak flow values had to show a diurnal variability of 20% or more during the run in period.

All patients were receiving treatment with inhaled steroids (daily dose 800 µg). None of the patients had had a recent respiratory tract infection and no patient had taken systemic glucocorticosteroids during the three months before the start of the run in phase. Plasma cortisol levels before and after a short Synacthen test⁹ had to be in the normal range. All patients gave their informed consent and the study protocol was approved by the local medical ethical committee.

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Table 1 Mean (SD) and range of baseline characteristics of the 17 patients

	Group 1	Group 2
No. of patients	8	9
Age (y)	37 (18–49)	41 (16–68)
M:F	7:1	5:4
Non-smokers:ex-smokers	5:3	5:4
FEV ₁ (% predicted)	86 (18) (46–101)	83 (18) (60–127)
Geometric mean PC ₂₀ histamine (mg/ml)	0.25 (95% CI 0.11 to 0.65)	0.25 (95% CI 0.09 to 0.64)
PEF morning (% predicted)	86 (20) (45–108)	77 (18) (44–98)

FEV₁ = forced expiratory volume in one second; PC₂₀ histamine = provocative dose of histamine producing a 20% fall in FEV₁; PEF = peak expiratory flow rate. Group 1 started with beclomethasone followed by prednisone; group 2 started with prednisone followed by beclomethasone.

STUDY DESIGN

The comparison between beclomethasone and prednisone was carried out as a randomised double blind crossover study using the double dummy technique. Each treatment period lasted four weeks. The first period was a single blind run in period of two weeks in which the patients received two placebo tablets in the morning and four placebo puffs twice daily. In the second period (four weeks, first treatment phase) one group received four puffs of beclomethasone dipropionate 250 µg twice daily and two placebo tablets in the morning, and the other group received two 5 mg prednisone tablets in the morning and four placebo puffs twice daily. In the third period (four weeks, washout) both groups received placebo tablets and placebo inhaler, and in the fourth period (four weeks, second treatment phase) the medication of the first treatment phase was crossed over. The study ended with a four week washout period with placebo medication as in the third period.

During the whole study the patients used β₂ agonists as needed for the immediate relief of their symptoms and the control of their asthma. Ipratropium bromide, if necessary combined with sustained release theophyllines, was allowed as concomitant medication when given in a constant dose throughout the study.

MEASUREMENTS

Before and after each period lung function and bronchial responsiveness were assessed. FEV₁ and the slow inspiratory vital capacity (SVC) were measured with a water sealed spirometer (Lode BV d75, the Netherlands). These measurements were taken at the same time of day between 9 am and 10 am. Bronchial hyper-responsiveness was expressed as the provocative dose of histamine producing a 20% fall in baseline FEV₁ (PC₂₀ histamine, de Vries method; inhalation of histamine during 30 seconds; normal values 32 mg/ml or higher).¹⁰ During the same visit the peak expiratory flow (PEF) was obtained from a flow-volume curve (Pneumoscreen, Jaeger). During the whole study PEF was measured at home at the same time every morning and evening before taking a β₂ agonist using a mini Wright peak flow meter. The best of three attempts was used for analysis. Pulmonary symptoms including dyspnoea, cough, sputum production, exercise limitation, and disturbed sleep were recorded

on a diary card and assessed on a five point scale (0 = no symptoms, 4 = severe symptoms).

Plasma cortisol levels were measured and a short Synacthen test⁹ was performed in an outpatient setting between 8.30 and 9.00 am on visits before and after each treatment phase. Blood samples for measurement of basal plasma cortisol levels were taken after a 15 minute rest with patients having fasted since midnight. Thirty minutes after intramuscular injection of 250 µg ACTH cortisol measurements were repeated. Cortisol levels were determined by enzyme immunoassay (ENDAB cortisol kit).

STATISTICAL ANALYSIS

The within patient differences between the beginning and end of treatment with beclomethasone dipropionate and prednisone (second to fourth periods) were compared between the two treatment order groups by the Mann-Whitney test. PC₂₀ values were analysed after log transformation. For testing residual effects of treatment at four weeks within patient differences between the two placebo periods (end of the third period to end of the fifth period) were compared between the two groups by the Mann-Whitney test. For testing residual effects of treatment at eight weeks within patient totals at the end of the two treatment periods (end of second period to end of fourth period) were compared between the two groups by the Mann-Whitney test.

Results

There were no significant differences in baseline values of PC₂₀ histamine, PEF, or FEV₁ between the two groups at the start of each treatment period (table 1). No statistically significant residual effects were found at four or eight weeks. There were no significant period effects. The results of the mean baseline values and mean values after treatment are given in table 2. There was a trend for PC₂₀ histamine to be higher in patients receiving beclomethasone dipropionate than in those receiving prednisone (0.43 mg/ml after prednisone and 0.76 mg/ml after beclomethasone dipropionate, *p* = 0.06, figure, table 2). FEV₁ (% predicted) showed an increase after both treatments with no significant difference between the two treatments. Morning PEF (diary cards) was higher after beclomethasone dipropionate than after prednisone (*p* < 0.05). The evening PEF (diary cards) and PEF (% predicted) in the lung function laboratory showed no significant difference between the two treatments. There was no difference in SVC measurements with either treatment (*p* = 0.74).

Basal cortisol levels at the start of both treatments were comparable (448 nmol/l and 445 nmol/l). There was no significant decrease after either treatment. The serum cortisol concentration after the stimulated cortisol test with the two treatments did not differ significantly. Pulmonary symptoms including dyspnoea, cough, sputum production, exercise

Table 2 Mean (SD) and range of lung function parameters and serum cortisol levels after treatment with beclomethasone dipropionate (BDP) and prednisone

	Before BDP	After BDP	Before prednisone	After prednisone	Comparison of BDP v prednisone
FEV ₁ (% predicted)	85 (18) (46-125)	93 (18) (69-134)	86 (16) (60-127)	91 (15) (67-123)	NS
FEV ₁ (l)	2.92 (0.97) (1.11-5.05)	3.21 (0.92) (1.98-4.87)	2.94 (0.83) (1.56-4.54)	3.10 (0.74) (2.10-4.53)	NS
SVC	4.74 (1.29) (2.84-7.81)	4.77 (1.36) (2.73-7.73)	4.67 (1.41) (2.82-7.92)	4.77 (1.37) (2.89-7.88)	NS
PEF (% predicted) morning	81 (18) (41-108)	92 (15) (71-124)	82 (15) (44-98)	86 (11) (68-108)	p < 0.05
Geometric mean PC ₂₀ histamine (mg/ml)	0.28 (0.05-1.70)	0.76 (0.07-8.00)	0.27 (0.06-1.80)	0.43 (0.10-6.50)	p = 0.06
	(95% CI 0.16 to 0.49)	(95% CI 0.38 to 1.52)	(95% CI 0.15 to 0.47)	(95% CI 0.25 to 0.73)	
Basal cortisol (nmol/l)	445 (127) (270-670)	442 (130) (230-810)	448 (199) (260-1110)	398 (194) (80-960)	NS
Stimulated cortisol (nmol/l)	725 (172) (510-1110)	668 (160) (370-920)	835 (303) (540-1830)	616 (203) (380-1180)	NS

FEV₁ = forced expiratory volume in one second; SVC = slow inspiratory vital capacity; PEF = peak expiratory flow rate; PC₂₀ histamine = provocative dose of histamine producing a 20% fall in FEV₁.

limitation, and disturbed sleep as recorded on a diary card showed a small but insignificant improvement after both treatments and there was no significant difference in the comparison of the treatments.

The within treatment analysis showed no effects of beclomethasone dipropionate on either basal or stimulated serum cortisol levels, but after treatment with prednisone stimulated cortisol levels were significantly lower ($p < 0.01$). This within treatment analysis also showed significant improvement in PC₂₀ histamine ($p = 0.01$), FEV₁ ($p = 0.02$), and morning PEF ($p = 0.01$) after treatment with beclomethasone dipropionate, but only FEV₁ increased significantly ($p = 0.02$) after treatment with prednisone.

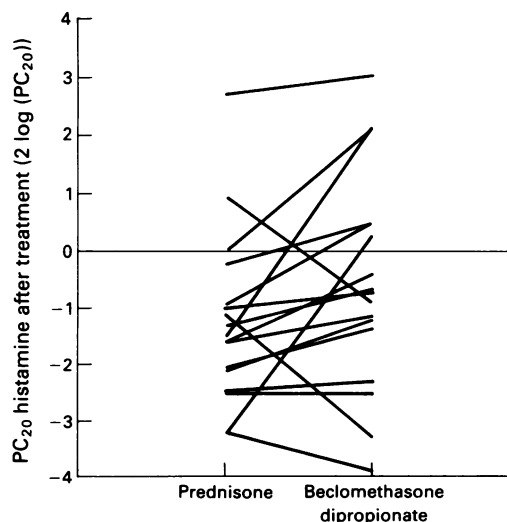
Discussion

Airway inflammation is thought to be an important cause of the increased bronchial responsiveness which is a hallmark of asthma. Studies have shown that there is a correlation between the severity of asthma and the degree of bronchial hyperresponsiveness. Reducing airway inflammation should therefore be of benefit in the treatment of asthmatic patients. Ryan *et al*¹¹ and Kraan *et al*¹⁰ both showed a decrease in bronchial hyperresponsiveness

after four weeks of treatment with beclomethasone (400 µg daily) and budesonide (400 µg daily) respectively when compared with β₂ agonists or placebo. This was accompanied by a significant increase in FEV₁. Jenkins and Woolcock⁶ showed a decrease in bronchial hyperresponsiveness with beclomethasone (1250 µg daily) but not with prednisone (12.5 mg daily) after three weeks of treatment. However, Wilmsmeyer *et al*⁷ found a comparable reduced responsiveness to histamine with 1000 µg beclomethasone and with 15 mg prednisone after two weeks of treatment.

In our group of asthmatic patients treatment with 2000 µg beclomethasone caused a significant increase in morning PEF and a trend to reduced bronchial hyperresponsiveness compared with treatment with 10 mg prednisone. An explanation for this might be the difference in potency of the two drugs. Because of the difference in pharmacokinetics of an inhaled and a systemic drug and the wide range of action of steroids in general, it is very difficult to estimate an overall equipotent dosage. Studies examining the prednisone sparing effect of inhaled beclomethasone suggest the effect on histamine provocation of 100 µg beclomethasone to be comparable to that of 1 mg prednisone.⁶ In terms of FEV₁, a clinical parameter, this study shows that both drugs, 2000 µg beclomethasone dipropionate and 10 mg prednisone, result in significant improvement. The equal results in FEV₁ cannot be explained by a lack of capacity to improve and could lead to the conclusion that in these doses the drugs are clinically comparable.

Another important difference might be the time of drug administration. To prevent adverse effects prednisone is generally given in the morning. The inhaled corticosteroids are given in two doses daily. In particular, the evening dose of beclomethasone dipropionate may be responsible for the difference in effect of beclomethasone and prednisone on the PC₂₀ and morning PEF. In support of this, Mohiuddin and Martin¹² showed that patients with allergic asthma are more susceptible to developing a late asthmatic response after allergen provocation in the evening than in the morning. The evening late asthmatic response also occurs sooner, is more severe, and causes a more prolonged decrease in bronchial responsiveness.¹² Prevention of the inflammatory ac-



PC₂₀ histamine levels after treatment with prednisone and beclomethasone dipropionate.

tivity of a late asthmatic response during the night is important for long term reduction of bronchial hyperresponsiveness¹³ and also diminishes nocturnal and early morning symptoms. Bronchial hyperresponsiveness and nocturnal and early morning symptoms were monitored in this study by PC₂₀ histamine and morning PEF. PC₂₀ histamine and morning PEF indeed showed an improvement in patients receiving beclomethasone dipropionate.

It is accepted that the optimal effect of inhaled steroids is achieved by regular treatment for several weeks or months. However, Vathenen *et al* recently showed that some effect can already be detected six hours after administration of a single dose of an inhaled steroid.¹⁴ It may be possible, therefore, that administration of beclomethasone dipropionate in the evening contributes to the protection of the critical nocturnal period and to the maintenance of decreased bronchial responsiveness in asthmatic patients.

The within treatment analysis shows, in contrast to the lack of effect on the basal cortisol level, a significant decrease of the stimulated cortisol level after prednisone treatment and no decrease after treatment with beclomethasone dipropionate. Other studies also show little influence of beclomethasone in doses up to 1500 µg on the hypothalamic-pituitary-adrenal (HPA) axis.¹⁵ This differs from the data of Wilmsmeyer *et al*⁷ who found a decrease in the stimulated serum cortisol level with prednisone as well as with beclomethasone dipropionate, although the dose of beclomethasone was only 1000 µg daily for two weeks. A possible explanation could be that they selected patients who had never needed corticosteroids and the treatment period was only two weeks. This effect would probably diminish after some weeks of treatment when a steady state was reached.

The observation that a commonly prescribed dose of oral corticosteroids in moderate to severe asthmatic patients already has an effect on the stimulated cortisol level indicates the advantages of inhaled treatment. It seems clear that the side effects of inhalation treatment such as hoarseness or risk of oral candidiasis are of less importance than the influence of oral glucocorticosteroids on the HPA axis.

We conclude that beclomethasone dipropionate 1000 µg twice daily has a slightly greater effect in this population of asthmatic patients than 10 mg of prednisone once a day, as demonstrated by a greater improvement in morning PEF and a trend to a reduction in bronchial hyperresponsiveness. Inhaled beclomethasone dipropionate has less effect on adrenocortical function than does prednisone.

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