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Effect of prednisone and beclomethasone diproprionate on airway responsiveness in asthma: a comparative study

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ABSTRACT To examine the effect of corticosteroids on bronchial hyperresponsiveness, a randomised, double dummy, single blind crossover study was performed in 18 subjects with chronic asthma, comparing the effect of three weeks' treatment with inhaled beclomethasone dipropionate, 1200 μg daily, and oral prednisone 12·5 mg daily. The 12 week study began with a three week run in period of baseline treatment, which was continued unchanged throughout the study, and the two treatment periods were separated by a three week washout period. Patients kept daily Airflometer readings and attended the laboratory every three weeks for spirometry and a histamine inhalation test for determining the provocative dose of histamine causing a 20% fall in FEV_1 (PD_{20}). The mean FEV_1 at the start was 1·9 litres (56% predicted). There was no significant change in PD_{20} with prednisone treatment, the mean PD_{20} being 0·56 and 0·59 μmol before and after treatment. There was, however, a significant improvement in PD_{20} with beclomethasone dipropionate treatment, the geometric mean PD_{20} being 0·38 and 1·01 μmol before and after treatment ($p < 0·001$). There was a small but significant improvement in mean FEV_1 after beclomethasone dipropionate treatment—from 1·9 to 2·2 litres—but no change after prednisone. Both medications produced significant and similar improvements in morning and evening Airflometer readings, post-bronchodilator improvement, and diurnal variation. Thus at doses that had similar beneficial effects on lung function beclomethasone dipropionate caused a significant improvement in bronchial hyperresponsiveness whereas prednisone caused no change. The superior topical anti-inflammatory effect of beclomethasone dipropionate may account for the different effects on bronchial hyperresponsiveness.

Although the mechanisms underlying bronchial hyperresponsiveness in asthma are still poorly understood, there is increasing evidence that airway inflammation has a major role in its development and maintenance.[1-3] Corticosteroids have been shown to diminish bronchial hyperresponsiveness caused by methacholine when this is given orally in high doses[4 5] and to reverse allergen induced increases in responsiveness.[6] Several studies, however, have failed to show any effect of oral corticosteroids on bronchial hyperresponsiveness.[7 8] More recent studies suggest that inhaled corticosteroids may be more effective in reducing it, although the magnitude of response in different studies has been variable.[9-11]

As no prospective study of the effect of equipotent doses of oral and inhaled corticosteroids has been performed, the present study was designed to compare the relative efficacy of an inhaled corticosteroid (beclomethasone dipropionate) with an oral corticosteroid (prednisone) in reducing bronchial hyperresponsiveness in subjects with moderately severe asthma. Patients kept a daily record of morning and evening Airflometer readings recorded before and 15 minutes after taking a bronchodilator. The Airflometer is a portable home monitoring device requiring a forced vital capacity manoeuvre to obtain a reading. It has been shown to give reproducible results that correlate closely with spirometric indices incorporating both FEV_1 and FVC. The reading is influenced by both expiratory volume and flow rate.[12]

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Methods

SUBJECTS

Eighteen asthmatic subjects with increased bronchial responsiveness to histamine and acute reversibility of FEV_1 of more than 15% in response to inhaled β_2

agonists entered the study (table 1). Geometric mean PD_{20} was 0·38 (range 0·03–3·0) μmol. All were maintained on regular inhaled salbutamol and beclomethasone dipropionate (400 μg daily), and were clinically stable at the time of entry. Four subjects were taking a daily maintenance dose of prednisone of 5 mg or less.

STUDY DESIGN

The study was conducted over 12 weeks and five histamine inhalation tests were performed at three weekly intervals. After a three week baseline period patients were randomised into two treatment groups, A and B. Group A received beclomethasone dipropionate 1200 μg daily (six puffs four times a day) and two and a half placebo tablets daily for three weeks, and group B received prednisone 12·5 mg daily (two and a half tablets) and placebo aerosol (six puffs four times a day) for three weeks.

After a further three week washout (no trial medication), patients took the alternative treatment for a final three weeks. Subjects continued with their background treatment throughout the study and the trial medications were added to this. Thus the maximum dose of beclomethasone dipropionate was 1600 μg (400 + 1200 μg) daily and of prednisone 17·5 mg daily in the four patients dependent on oral corticosteroid. All other patients took beclomethasone dipropionate 1200 μg daily and prednisone 12·5 mg. Trial treatments were administered in single blind manner.

THE TESTS

Subjects visited the laboratory for spirometric testing and a histamine inhalation test every three weeks, at the same time each day for each individual. Before each visit trial medications, inhaled β_2 agonists, and beclomethasone dipropionate were withheld for eight hours. After baseline spirometry a histamine inhalation test was carried out according to the method of Yan *et al.*[13] Aerosols were generated by a hand held De Vilbiss No 40 glass nebuliser. After measurement of baseline FEV_1 subjects inhaled three breaths of normal saline and the FEV_1 was measured twice at 60 seconds. Histamine was then administered, progressing in doubling doses from a starting dose of 0·03 μmol. Two FEV_1 manoeuvres were carried out 60 seconds after each dose and followed by the next histamine dose. The challenge was stopped when the FEV_1 fell by 20% or more of the post-saline value, or when the maximum number of doses had been given (7·8 μmol total dose). Results were expressed as the dose of histamine producing a 20% fall in FEV_1 (PD_{20}), calculated from the log dose-response curve.

Table 1 *Characteristics of the patients*

Number	18
Age (y): mean (range)	42 (22–64)
Sex	9F, 9M
FEV_1 (% predicted): mean (range)	56·1 (31–75)
PD_{20} (μmol): geometric mean (range)	0·38 (0·02–2·8)
Regular previous treatment:	
No of patients	
Salbutamol, beclomethasone	3
Salbutamol, beclomethasone, theophylline	8
Salbutamol, beclomethasone, sodium cromoglycate	3
Salbutamol, beclomethasone, theophylline, oral corticosteroids	4

STATISTICAL ANALYSIS

PD_{20} values were logarithmically transformed for comparison between treatments. Changes in PD_{20}, FEV_1, and Airflometer readings were assessed by analysis of variance. Airflometer readings were compared by calculating four mean weekly Airflometer readings—for morning and evening, before and after bronchodilator, for each treatment period. In addition, mean diurnal variability was calculated for each day as (maximum–minimum daily AFM reading) ÷ maximum daily AFM reading, and a mean was calculated for each three week treatment period.

Results

Geometric mean PD_{20} values at the start of the oral and inhaled treatment periods were not significantly different (table 2). There was a significant increase in geometric mean PD_{20} during the beclomethasone dipropionate treatment period—from 0·38 μmol at the beginning to 1·01 μmol after three weeks ($p < 0·001$). The mean PD_{20} for the subjects taking prednisone did not change, being 0·56 μmol initially and 0·59 μmol after three weeks (table 2, fig 1). No treatment effect was identified when PD_{20} at completion of the baseline period was compared with values at the end of the washout period (geometric mean PD_{20} being 0·43 and 0·48 μmol respectively).

Mean FEV_1 values showed a small but significant improvement during the beclomethasone treatment period from 1·9 to 2·2 litres. There was no change in FEV_1 during the prednisone treatment period, the mean FEV_1 at the beginning and end being 2·0 litres (table 3, fig 2). Morning Airflometer readings before and after bronchodilator were, however, significantly higher during both beclomethasone and prednisone treatment than the baseline values. The mean morning Airflometer readings were 60·1 with beclomethasone and 60·8 with prednisone, compared with 44·3 during the baseline period ($p < 0·001$). Post-bronchodilator morning Airflometer readings rose to 77·2 with beclomethasone and 78·6 with prednisone ($p < 0·01$). The mean evening Airflometer readings were also higher with prednisone (71·5) and beclomethasone

Table 2 *Provocative dose (μmol) of histamine causing a 20% fall in FEV_1 (PD_{20}) for 18 subjects during the 12 week study period*

Patient No	Given first	Baseline		Oral steroid		Inhaled steroid	
		Beginning	End	Beginning	End	Beginning	End
1*	Oral	2·8	2·8	2·8	2·2	4·0	2·4
2*	Oral	0·65	0·85	0·85	2·6	0·98	>10·0
3	Oral	0·3	1·1	1·1	1·1	0·7	1·7
4	Oral	0·8	1·4	0·28	0·65	0·29	0·75
5*	Oral	0·65	0·38	0·38	0·16	0·24	0·16
6	Oral	0·07	0·14	0·14	0·3	0·1	0·29
7	Oral	—	0·23	0·2	0·21	0·7	3·91
8	Oral	1·2	1·4	1·4	2·0	0·55	2·5
9	Inhaled	0·4	0·4	0·6	0·5	0·4	0·8
10	Inhaled	0·53	0·28	0·33	0·05	0·28	0·50
11*	Inhaled	0·6	0·6	1·8	1·0	0·6	0·34
12	Inhaled	1·0	1·0	3·0	3·0	1·0	5·0
13	Oral	0·04	0·13	0·13	0·15	0·21	0·32
14	Oral	—	0·32	0·32	0·27	0·14	1·2
15	Inhaled	2·8	3·0	>10·0	3·0	>10·0	10·0
16	Inhaled	0·06	0·04	0·28	0·65	0·04	0·40
17	Inhaled	0·02	0·03	0·05	0·20	0·03	0·24
18	Inhaled	—	0·5	0·5	0·85	0·15	0·35
Geometric mean		0·38	0·43‡	0·56	0·59‡	0·38	1·01†
95% confidence interval		0·02–7·69	0·03–6·17	0·04–8·50	0·05–6·7	0·02–7·38	0·09–15·9

*Patients taking maintenance prednisone ≤5 mg/day.
†$p < 0·01$.
‡ Not significant in the PD_{20} comparison before and after each study period.

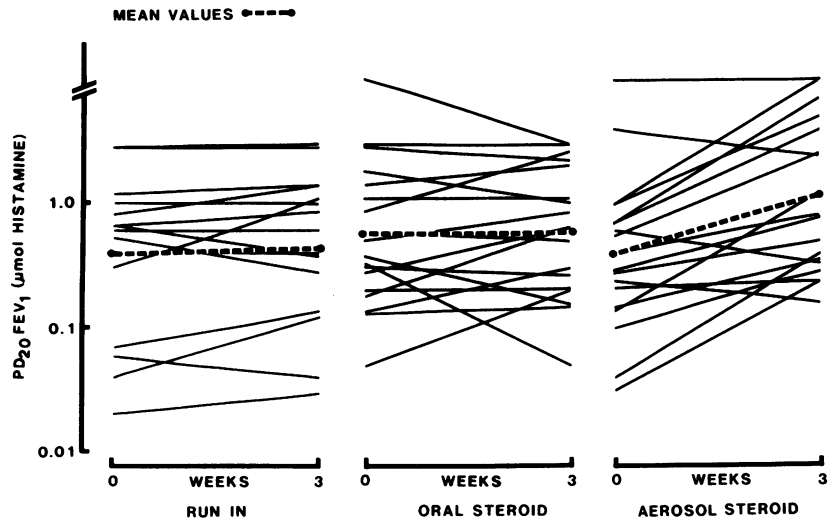

Fig 1 *Doses of histamine (μmol) producing a 20% fall in FEV_1 (PD_{20}) at the beginning and end of the baseline, prednisone, and beclomethasone diproprionate treatment periods.*

(69·6) but only for pre-bronchodilator readings ($p < 0·05$). Airflometer diurnal variation was significantly less during prednisone and beclomethasone treatment than during the baseline period, but no different between the prednisone and beclomethasone treatment periods (table 3).

There was no correlation between improvement in PD_{20} with beclomethasone and either baseline PD_{20} or FEV_1 predicted at the start of the study.

Discussion

Although the efficacy of corticosteroids in the treatment of asthma is widely accepted,[14 15] the mechanisms by which this effect is achieved have yet to be fully elucidated. Several recent studies[9–11 16] have indicated that the inhaled corticosteroids beclomethasone dipropionate and budesonide can diminish the bronchial hyperresponsiveness caused by histamine

Table 3 *Mean (SD) changes in lung function (Airflometer (AFM) units) over each three week period in 18 subjects with asthma*

	Baseline	*Oral corticosteroids*	*Inhaled corticosteroids*
Morning AFM pre-bronchodilator	44·3 (40·8)	60·8 (48·0)*	60·1 (46·9)*
Morning AFM post-bronchodilator	67·2 (53·2)	78·6 (54·3)†	77·2 (52·1)†
Evening AFM pre-bronchodilator	63·2 (52·5)	71·5 (44·3)‡	69·6 (54·4)‡
Evening AFM post-bronchodilator	78·4 (57·8)	85·8 (58·4)	82·1 (55·2)
Diurnal variation	0·46 (0·16)	0·40 (0·14)§	0·38 (0·15)§
Mean morning post-bronchodilator (% change)	51·7 (35·0)	29·3 (23·6)	28·0 (22·3)
Mean evening post-bronchodilator (% change)	24·1 (22·7)	20·0 (17·3)	18·0 (13·7)
Mean FEV_1 (l)	1·9 (0·7)	2·0 (0·8)	2·2 (0·8)

*p < 0·001; †p < 0·01; ‡p < 0·05; §p < 0·025, by comparison with baseline values.

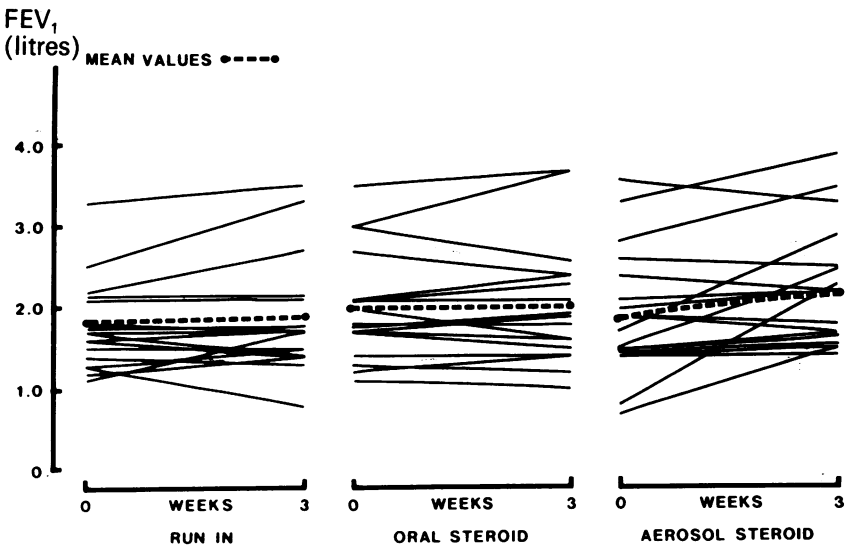

Fig 2 *FEV_1 (l) measurements at the beginning and end of the baseline, prednisone, and beclomethasone diproprionate treatment periods.*

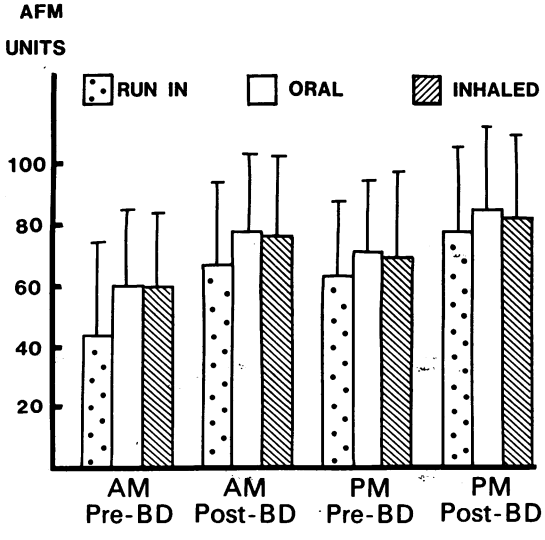

Fig 3 *Mean morning (AM) and evening (PM) Airflowmeter (AFM) readings in 18 subjects during baseline (run in), prednisone, and beclomethasone diproprionate (BD) treatment periods.*

and methacholine, and this may have a major role in the improvement in symptoms produced by corticosteroids. The findings of the present study are in keeping with the results of these studies, and show a greater increase in PD_{20} in subjects taking beclomethasone than previously reported.[9 10]

Although oral corticosteroids are clearly beneficial in the management of unstable asthma,[14] paradoxically many studies have failed to show a reduction in bronchial hyperresponsiveness[7 8 17] except when moderately high doses have been given.[5] In the present study the dose of 12·5 mg prednisone daily was chosen to approximate the effect of beclomethasone 1200 μg daily on symptoms and lung function. Although the true equipotent dose of the two drugs is not known and will vary according to the target organ, the dose was determined from studies examining the prednisone sparing effect of inhaled beclomethasone dipropionate in patients with steroid dependent asthma.[18–20] In these studies steroid dependent asthmatic patients were able to reduce their oral prednisone dose by 4–8 mg daily when they started taking beclomethasone 400–800 μg daily, suggesting a relationship of

about 1 mg:100 μg for oral prednisone, so that about 100 μg of inhaled beclomethasone dipropionate is equivalent to the effect of 1 mg of prednisone. The present data indicate that in terms of daily lung function, as measured by the Airflometer, these doses of beclomethasone and prednisone resulted in similar levels of improvement. Although mean FEV_1 was significantly higher with inhaled beclomethasone than with prednisone such a small change is unlikely to influence the measurement of airway responsiveness. But although beclomethasone produced a reduction in responsiveness to histamine prednisone did not. It has been suggested by some authors[6 7] that bronchial hyperresponsiveness may have two components—"primary" hyperresponsiveness and "induced" hyperresponsiveness. They propose that background or primary bronchial hyperresponsiveness is relatively insensitive to corticosteroids, whereas induced bronchial hyperresponsiveness (such as occurs during allergen exposure or after exposure to chemical sensitisers) is responsive to corticosteroids.[6 21–23] This hypothesis would explain why corticosteroids do not reduce baseline bronchial hyperresponsiveness in subjects with stable asthma[7 8] even though they reduce[21 22] or reverse allergen induced increases in hyperresponsiveness.[6] Our results suggest that the extent to which corticosteroids reduce bronchial hyperresponsiveness may depend on which corticosteroid is given and on the route of delivery in addition to dose. Indeed, higher doses of orally or parenterally administered steroids have been shown to reduce bronchial hyperresponsiveness, but are clearly undesirable in the long term management of asthma. The dose of beclomethasone chosen in this study is not known to cause serious steroid related side effects. Several subjects showed a shift from increased bronchial hyperresponsiveness to a level within the normal non-asthmatic range, indicating that primary bronchial hyperresponsiveness is highly amenable to corticosteroid treatment.

It has also been postulated that the reduction in bronchial hyperresponsiveness produced by inhaled corticosteroid might result from the associated improvement in airway calibre. The study of Ryan *et al*[10] suggests that this is not the case in subjects with mild asthma, and the present study confirms that it is not so in subjects with more severe asthma. Although these subjects did show significant improvement in daily Airflometer readings while taking both the medications being studied, the small improvement in FEV_1 while they were taking beclomethasone would not be expected to have a significant effect on bronchial hyperresponsiveness. The failure of this dose of prednisone to modify bronchial hyperresponsiveness in subjects who were responsive to beclomethasone occurred despite a significant improvement in morning and evening Airflometer readings and reduced diurnal variation in the readings, which was similar to the effect of beclomethasone. The lack of improvement in bronchial hyperresponsiveness from prednisone may relate to the absence of change in baseline FEV_1, suggesting that perhaps too small a dose of prednisone was chosen for comparison with beclomethasone. Several studies, however, have been unable to show a significant relationship between resting airway calibre and bronchial hyperresponsiveness in asthma,[24 25] the exceptions showing only a weak positive relationship.[26] Possibly the mechanisms by which lung function is improved by corticosteroids are not the same as those resulting in a change in bronchial hyperresponsiveness. Improved lung function may result from inhibition of mediator release from acute inflammatory cells,[27 28] reduction in oedema[29] and mucus hypersecretion,[30] and inhibition of cellular migration in addition to direct effects on bronchial smooth muscle receptors.[31] A reduction in bronchial hyperresponsiveness, however, may specifically result from a concentration of one or more of these effects in the bronchial epithelium or cells close to the bronchial lumen.[32–34] While the different effect of oral and inhaled corticosteroids on bronchial hyperresponsiveness in our study may be due to choice of dose, it is consistent with studies indicating that the bronchial epithelium may be an important participant in the development and maintenance of bronchial hyperresponsiveness in asthma.[34 37] This is also in keeping with the observation that budesonide, a more topically potent corticosteroid than beclomethasone,[35] can produce larger shifts in bronchial hyperresponsiveness than beclomethasone.[11] Oral corticosteroids may cause an improvement in lung function through similar effects concentrated at other sites, possibly at the submucosal level rather than on cells within or at the airway lumen. Prednisone is a relatively weak topical anti-inflammatory agent,[35] and even with adequate penetration of the bronchial mucosa and submucosa it may not modify local inflammatory processes to the same extent as beclomethasone. The poor penetration of prednisone into bronchoalveolar lavage fluid suggests that the drug may have limited access to the bronchial epithelium.[36]

The differences between oral and aerosol corticosteroids could reflect differences in their site of action, changes in bronchial hyperresponsiveness reflecting changes mainly in large airways. This is unlikely for several reasons. Oral corticosteroids are unlikely to affect only small airways, and indeed both oral and aerosol corticosteroids produced significant improvements in Airflometer readings, suggesting that the effect of both drugs was widespread throughout the airways. In addition, it has been shown that there are no differences in PD_{20} when histamine is deposited

preferentially in either the large or the small airways.[38 39]

Thus in this study beclomethasone dipropionate 1200 μg daily produced changes in Airflometer readings similar to those of prednisone 12·5 mg daily. This dose of beclomethasone produced a slightly greater improvement in FEV_1 than prednisone and a significant change in bronchial hyperresponsiveness, which prednisone did not. Further studies are required to elucidate the mechanisms of the change in bronchial hyperresponsiveness effected by beclomethasone.

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