

Comparison of two high dose corticosteroid aerosol treatments, beclomethasone dipropionate (1500 $\mu\text{g}/\text{day}$) and budesonide (1600 $\mu\text{g}/\text{day}$), for chronic asthma

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ABSTRACT Twenty eight patients with chronic asthma took part in a double blind single crossover controlled trial of inhaled budesonide and inhaled beclomethasone dipropionate, using high doses of 1600 μg and 1500 μg daily respectively. Both drugs were administered by pressurised aerosol inhaler; the inhaler containing budesonide and its matching placebo were fitted with a collapsible spacer device. There was no significant difference in the control of asthma during the two six week treatment periods. There was no significant difference in FEV₁ and forced vital capacity after four and six weeks of treatment or in mean morning and evening peak expiratory flow rates for the last 21 days of treatment. There was a small but statistically significant reduction in the daytime wheeze score while they were taking high dose budesonide but there was no difference for daytime activity, cough, and night symptoms. The mean basal cortisol concentrations were significantly lower after six weeks of high dose treatment than before treatment (budesonide $p < 0.01$, beclomethasone $p < 0.05$). There was no difference between mean basal cortisol values after six weeks of high dose treatment, and there was no effect on the rise of cortisol obtained after a short tetracosactrin test. High dose inhaled corticosteroids produced few side effects and were well tolerated.

The corticosteroid budesonide, which became available in an inhaler form for the treatment of asthma relatively recently, has been shown to be as effective in controlling asthma at dosages of 200 μg twice daily as beclomethasone dipropionate at dosages of 100 μg four times a day.¹ At these low dosages there are no significant side effects and there is no evidence of adrenal suppression as indicated by 9 am plasma cortisol concentration and the response to a short tetracosactrin (synacthen) test. There is only a limited amount of information on the inhalation of higher doses of these drugs in the treatment of severe chronic asthma.

The early studies of Gaddie² suggested that increasing the daily dose of beclomethasone to 1600 μg produced no improvement in FEV₁ or forced

vital capacity (FVC) but that there was adrenal suppression as judged by a significantly lower 30 minutes' stimulated cortisol concentration after a short tetracosactrin test when patients were having this dose than when they were taking lower doses. Several subsequent studies have shown, however, that use of higher doses leads to improved control of asthma. Smith and Hodson³ in a retrospective study found that 27% of steroid dependent asthmatic patients were able to stop oral steroid treatment on the introduction of inhaled treatment with high doses of beclomethasone, usually of 1000 μg or more daily, and that 39% of steroid dependent patients were able to reduce their oral steroid treatment. These workers also found⁴ that in patients taking long term inhaled beclomethasone at a daily dose of 2000 μg there was evidence of adrenal suppression as measured by a short tetracosactrin test.

We have conducted a prospective study in patients with chronic asthma, comparing the efficacy of beclomethasone 1500 μg daily with budesonide

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1600 µg daily in the control of their asthma. We also assessed the incidence of side effects, and looked for evidence of adrenal suppression by using the short tetracosactrin test.

Methods

Twenty eight patients with chronic asthma (20 male) entered the study (mean age 54, range 19–72 years). They were all attending outpatient asthma clinics regularly and their attending physician considered their asthma to be poorly controlled and to require further treatment. All patients showed at least 15% improvement in peak expiratory flow (PEF) after inhalation of two puffs (200 µg) of aerosolised salbutamol. Four patients were smokers and one patient fulfilled the Medical Research Council criteria for chronic bronchitis. All patients had demonstrated a good inhaler technique and none was taking oral corticosteroids either at the time of the study or for at least two months before entry to the study. The patients were allocated randomly to a crossover study of two treatment periods, A and B, each of six weeks. Treatment A consisted of three puffs of beclomethasone (750 µg) and four puffs of placebo budesonide twice daily, and treatment B consisted of four puffs (800 µg) of budesonide and three puffs of placebo beclomethasone twice daily. The last 16 patients recruited were also studied while they were having their existing treatment for two weeks before random allocation.

Budesonide was delivered by means of a collapsible spacer device as this was the only form available for clinical use at the time of the study. Patients attended the outpatient clinic at two weekly intervals, when FEV₁ and forced vital capacity were measured. A short tetracosactrin test was performed on entry to the randomised part of the trial and after six weeks (at crossover) and 12 weeks (at the end of the study) of high dose treatment. An intramuscular injection of 0.25 mg tetracosactrin was given between 9 am and 10 am after a venous blood sample had been taken for estimation of basal plasma cortisol concentration, and a further sample was taken 30 minutes later. Plasma cortisol concentration was assayed according to the method of Riad-Fahmy.⁵ Patients were issued with diary cards to record daily symptoms of cough, day wheeze, night symptoms, and daytime activity on a rating scale. They recorded the PEF (the best of three attempts) on a Wright's mini peak flow meter on rising and at 7 pm.

Any side effects were noted at clinic visits. If a patient reported a sore throat or features suggesting oropharyngeal infection with *Candida albicans* a throat swab was taken and appropriate treatment with antifungal agents was started if judged clinically

necessary. Bronchodilators for inhalation were allowed freely and their daily usage was recorded. The use of oral bronchodilators and any other treatment remained unchanged. If a patient had an exacerbation of asthma requiring oral steroid treatment, the patient was withdrawn from the study and re-entered the next treatment period after four weeks without oral steroids.

The full blood count, differential white cell count, and platelet count and plasma, urea, and electrolyte concentrations were determined and liver function tests were carried out at the same time as the short tetracosactrin test was performed.

STATISTICAL METHODS

Comparison of beclomethasone with budesonide in high dosage

FEV₁ and FVC at four and six weeks were compared by means of paired Student's *t* test (single results being discarded) and morning and evening PEF for the last 21 days of each treatment by means of repeated measures of analysis of variance. The Wilcoxon signed rank test was used to compare daytime activity, cough, and night symptoms, and the Mann-Whitney test to compare the use of inhaled bronchodilator.

Comparison of high dose with existing treatment

An analysis of variance (ANOVA) was used to compare morning and evening peak expiratory flow and daily usage of inhaler bronchodilator during the period of existing treatment and the last 21 days of the two treatment periods. Where significance differences were detected with ANOVA, suitable linear contrasts were used to examine differences between the three periods. Two tailed *t* tests were used with Duncan's correction for three means for all significance levels (*p* < 0.05 being taken as minimum significance level).

Results

COMPARISON OF BECLOMETHASONE WITH BUDESONIDE IN HIGH DOSAGE

During the 56 treatment periods in 28 patients there were three exacerbations of asthma requiring oral corticosteroid treatment, one during beclomethasone treatment and the other two during both treatments in the same patient. Both of these patients were excluded from the analysis. There was no significant difference between the two drug treatments in either FEV₁ or FVC at four and six weeks after the start of treatment (paired Student's *t* test; table 1). The mean daily dose of beclomethasone was 887.5 µg before entry to the study.

There was no significant difference between either

Table 1 FEV₁ and forced vital capacity (means with standard deviations in parentheses) at the start of the study and after four and six weeks of treatment with budesonide (BUD) or beclomethasone dipropionate (BDP)

	BUD	BDP
FEV ₁		
Start of study	1.85 (0.14) n = 27	
After four weeks' treatment	1.95 (0.16) n = 24*	1.96 (0.15) 26*
After six weeks' treatment	1.87 (0.16) n = 27	1.76 (0.13) 26*
Forced vital capacity		
Start of study	3.03 (0.17) n = 27	
After four weeks' treatment	3.07 (0.18) n = 24*	3.04 (0.17) 26*
After six weeks' treatment	2.90 (0.18) n = 27	2.82 (0.15) 26*

*In a few cases no recording was made because of prior use of inhaled bronchodilator.

morning or evening PEF for the last 21 days of each treatment (n = 26). By using the last three weeks of treatment for the comparisons no carryover effect of the previous treatment was seen. The mean (SEM) morning PEF for the last three weeks of treatment was 314.1 (4.0) l min⁻¹ during budesonide treatment and 311.2 (4.1) l min⁻¹ during beclomethasone treatment. The mean evening PEF for the last three weeks of treatment was 335.9 (3.9) l min⁻¹ during budesonide treatment and 334.0 (3.7) l min⁻¹ during beclomethasone treatment.

The evaluation of the last four weeks of each treatment session, compared by means of the Wilcoxon signed rank test, showed no significant difference for daytime activity, cough and night symptoms. Daytime wheeze was assessed by the patients as none, little, moderately bad, or severe and values from 1 = none to 4 = severe were assigned to these categories. An average daily score was calculated for the last four weeks of each treatment period for each patient. The daytime wheeze scores for the budesonide period were found to be significantly lower than those for the beclomethasone period (Wilcoxon signed rank test; p < 0.05). The median wheeze scores (ranges in parentheses) were 1.6 (1-2.2) for budesonide and 1.7 (1-3.1) for beclomethasone. Of the 26 patients

reporting on their daytime wheeze symptoms, 10 showed less severe symptoms in the budesonide than in the beclomethasone period; six of these patients showed improvement in their daytime wheeze symptoms on seven or more days. Eleven patients showed no difference in daytime wheeze and five, while doing better in the beclomethasone than in the budesonide period, showed an improvement on less than seven days.

The use of inhaled bronchodilator during the last 21 days of treatment was significantly different between treatments (Mann-Whitney test; p < 0.05), being greater during beclomethasone than during budesonide treatment. The median daily number of puffs of bronchodilator (range in parentheses) was 6.72 (0-22) for budesonide and 7.81 (0-26) for beclomethasone.

The mean basal cortisol concentrations were significantly lower after six weeks' treatment than before treatment (table 2) (n = 26, excluding patients who received prednisolone during the study; Student's *t* test; budesonide p < 0.01 and beclomethasone p < 0.05); and there was no significant difference between the mean basal cortisol values after six weeks' high dose treatment compared by means of Student's *t* test (n = 26). There was no effect of the rise of cortisol after tetracosactrin for any treatment. There was no relationship between previous oral corticosteroid treatment or the interval since treatment stopped and the values obtained in the tetracosactrin test.

Side effects of the treatment were all considered minimal by the patients and the attending physicians. There were six reports of sore throat (four budesonide, two beclomethasone); throat swabs were taken but only three grew *Candida albicans* (two budesonide, one beclomethasone). Eleven patients complained of a "cough with a spacer inhaler." Five patients while having placebo budesonide, four while having active budesonide, and two patients while having both placebo and active budesonide complained of an unpleasant taste of the spacer. Finally, one patient having active beclomethasone and one having active budesonide complained of retching. There were no requests to withdraw by the patients and none

Table 2 Cortisol values (nmol/l) obtained before and after synacthen: mean values (with standard errors in parentheses) for each of the treatment periods (n = 26), excluding those patients who received oral steroids during either of the treatment periods

	Start of study	Budesonide period	Beclomethasone period	Normal values
Basal plasma cortisol	309 (29)	222 (18)	248 (21)	170-690
Increment 30 min after synacthen	269 (27)	245 (13)	246 (18)	> 308
Plasma cortisol 30 min after synacthen	577 (36)	467 (18)	495 (20)	> 550

Conversion: SI to traditional units—Cortisol: 1 nmol/l = 0.036 µg.

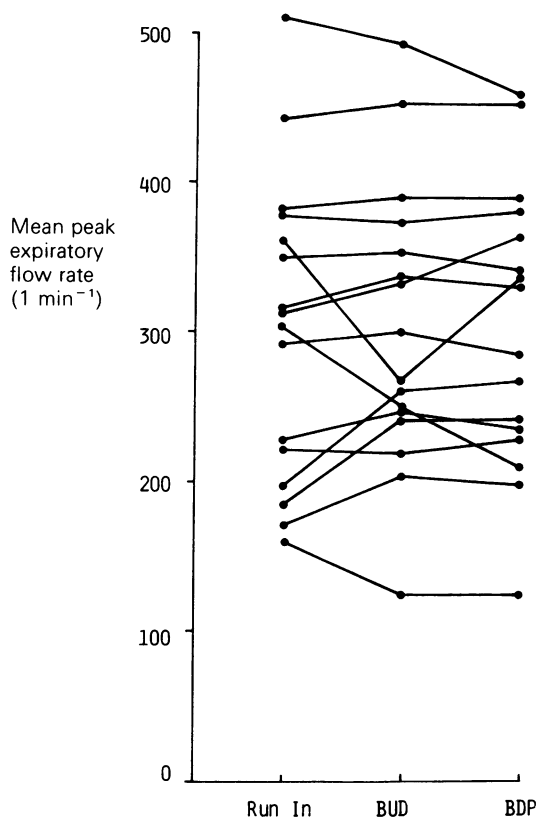


Fig 1 Comparison of morning peak expiratory flow (PEF) during 14 days of existing treatment and the last 21 days of each treatment period. High dose treatments were administered in random order but for clarity are shown in a fixed order.

required cessation of the treatment.

The haematological and biochemical measurements performed were unaffected by the high dose treatment.

COMPARISON OF HIGH DOSE WITH EXISTING TREATMENT

Nine of 16 patients showed a significantly higher value for at least one of the indices measured (morning peak expiratory flow, evening peak expiratory flow, daily inhaled bronchodilator usage) while taking high dose treatment than during their existing medication. Two patients showed a significant increase in both morning and evening PEF and a significant reduction in daily bronchodilator usage. Two patients showed a significant increase in morning and evening PEF only. Two patients showed a significant increase in evening PEF and a significant

reduction in daily bronchodilator usage and three patients showed only a significant reduction in daily bronchodilator usage. The mean daily dose of beclomethasone of the nine who showed improvement was 906 μg . Two patients showed no differences in PEF or daily bronchodilator usage. The three remaining patients showed ambiguous changes on changing to high dose treatment, with both a significant decrease in PEF and a reduction in daily bronchodilator usage. These results are summarised in figures 1-3.

Discussion

We have found no significant difference between budesonide (1600 μg daily) and beclomethasone (1500 μg daily) in controlling chronic asthma as assessed by spirometry after treatment and comparison of the

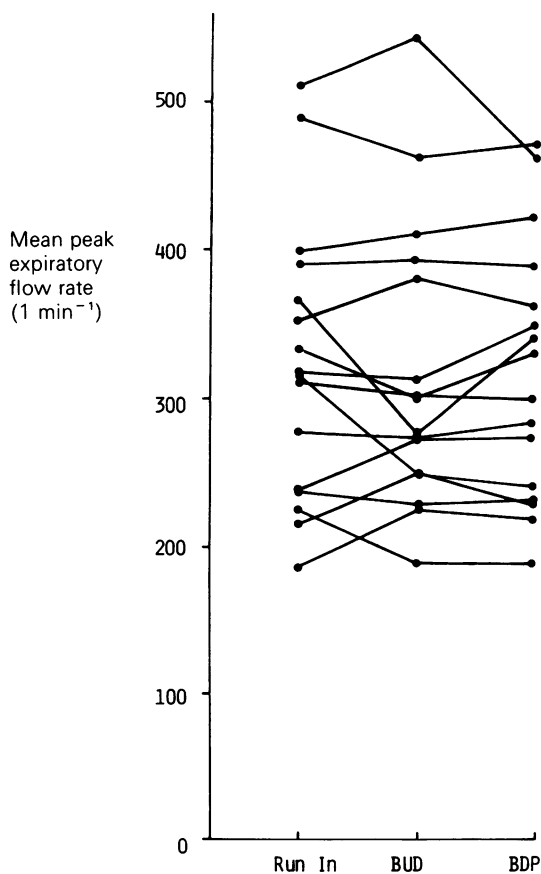


Fig 2 Comparison of evening peak expiratory flow (PEF) during 14 days of existing treatment and the last 21 days of each treatment period. High dose treatments were administered in random order but for clarity are shown in a fixed order.

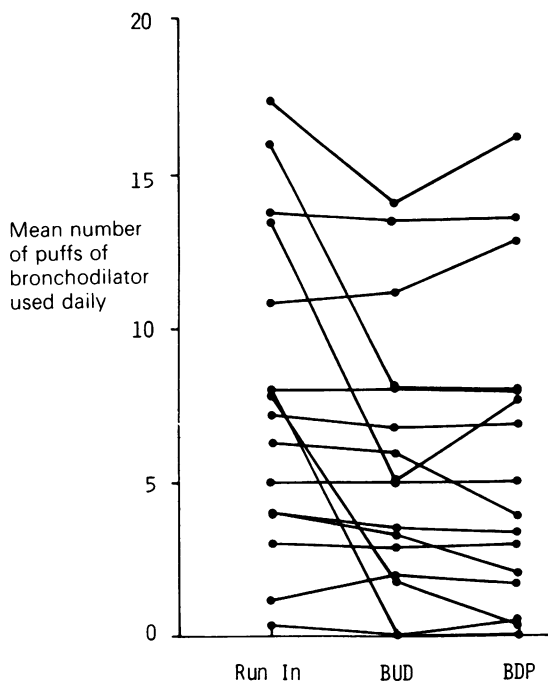


Fig 3 Comparison of daily inhaled bronchodilator use during 14 days on existing treatment and the last 21 days of each treatment period. High dose treatments were administered in random order but for clarity are shown in a fixed order.

PEF during the last 21 days of treatment. Because of the relatively small number of patients, the power of the study to detect a difference in ventilatory performance or in symptoms while they were having the two treatments is limited and a type II error could exist. We consider, however, that we are unlikely to have overlooked a major difference of clinical importance. Our findings are similar to those of Willey and coworkers,¹ who found that low dosages of daily budesonide (400 µg) were as effective as beclomethasone (400 µg). In the present study high dose budesonide was better than high dose beclomethasone at controlling day wheeze, and mean daily bronchodilator use was less with budesonide; but this may reflect the slightly different doses used and is likely to be a clinically small effect, only amounting to about one puff a day. Because of the differences in mode of delivery it is not possible to apportion benefit from budesonide between the spacer device and the drug.

Side effects were found to be minimal and we noted only three cases of oropharyngeal candidiasis, which easily resolved with conventional treatment. Other workers have found a relatively low incidence of oro-

pharyngeal candidiasis, although the incidence to a certain extent depends on the enthusiasm with which it is sought. Eleven patients complained spontaneously of a cough with the spacer in the placebo group. The propellant used in the budesonide inhaler is the same as that used in the terbutaline inhaler and there are no reports of this symptom with this inhaler. The cause of the cough is unclear.

The assessment of adrenal function in patients taking high dose inhaled steroids is problematical. Most workers use the short tetraacosactin test as a measure of adrenal function and reserve, and also as an indicator of subclinical systemic absorption. There are, however, no normal values for asthmatic patients who have not taken steroids. The insulin stress test is a more sophisticated assessment of the adrenal-pituitary axis, although it clearly cannot be performed as a routine procedure, but it will provide information about the whole axis. Basal adrenocorticotrophic hormone concentrations do not provide a measure of the response to stress and the metyrapone test is time consuming and not practical for an outpatient study.⁶

With these reservations we have used the short tetraacosactin test. We found a significant reduction in the morning basal cortisol concentrations when patients changed from existing treatment with beclomethasone at a mean daily dose of 887.5 µg to high dose treatment at a dose of 1500 µg and to budesonide at a dose of 1600 µg daily. All of these basal plasma cortisol concentrations are, however, still within the normal clinical range. Gaddie² found a significant reduction in the rise of cortisol after tetraacosactin stimulation after 1600 µg beclomethasone had been given for 28 days. We found no such effect on the rise, however, when patients changed to higher dosages. Costello and Clark⁷ suggested that there might be adrenal suppression at doses of 2000 µg/day of beclomethasone, but they had only three patients having this dosage. Smith and Hodson⁴ suggest that there is adrenal suppression at this dosage, but unfortunately they had only four patients taking 1500 µg/day of beclomethasone, so that it is not possible from their data to be sure at what dose of inhaled corticosteroid adrenal suppression starts.

Finally, is there any benefit in increasing the dose of inhaled corticosteroids to doses of 1600 µg/day (budesonide) and 1500 µg/day (beclomethasone) in patients with chronic asthma? This part of the study is uncontrolled, and therefore interpretation of the results should be made with caution. Nine patients, however, did improve with respect to at least one of the objective criteria when going on to high dose treatment (morning PEF, evening PEF, and daily bronchodilator usage). On these criteria only two patients were worse with high dose treatment. The

increase in the daily dose of corticosteroid, however, was less than twofold.

It would appear that many patients may benefit from high dose treatment, although it is important to monitor the response in the individual patient to be sure that there is benefit. Early studies by Gaddie did not find any benefit from increasing the dose of beclomethasone to 1600 $\mu\text{g}/\text{day}$, but subsequent studies have not confirmed this. Possibly their patients had no potential for improvement. More recently the retrospective study of Smith and Hodson showed that 27% of patients with chronic asthma could be taken completely off oral corticosteroid treatment when taking beclomethasone at a daily dose of 1000 μg . Thirty nine per cent of patients were able to reduce their daily dose of oral prednisolone by an average of 5.5 mg. They also found a significant improvement in peak expiratory flow rate and a reduction in the number of severe asthmatic attacks.

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