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Beclomethasone dipropionate dry-powder inhalation compared with conventional aerosol in chronic asthma

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Summary and conclusions

In a double-blind study beclomethasone dipropionate inhaled as a dry powder in doses of 100 μg four times daily and 150 μg four times daily was compared with the conventional aerosol dose of 100 μg four times daily in 20 outpatients with chronic asthma. Each of the three treatments was given for four weeks. The dry powder in a dose of 150 μg four times daily had advantages over the other two treatments in terms of FEV_1 and the number of exacerbations of asthma during the study. There were no adverse reactions to inhaling dry-powder beclomethasone.

It was concluded that this new way of administering the drug was effective in chronic asthma, and should allow most patients with chronic asthma who cannot use conventional pressurised aerosols efficiently to benefit from inhaled corticosteroid treatment.

Introduction

Many patients with chronic asthma have benefited from corticosteroid treatment by inhalation, since in this form the drugs are locally active and free from systemic side effects. Nevertheless, only patients who can use pressurised aerosols efficiently have been able to benefit from this route of administration. Many adult patients cannot use conventional pressurised inhalers correctly even after careful tuition,[1] and unfortunately, a high proportion are elderly patients in whom the side effects of systemic corticosteroid treatment, notably osteoporosis, are often more troublesome than in younger patients. Generally, young children have been denied the advantages of inhaled corticosteroids, since few can be taught to inhale fluorocarbon-propelled drug aerosols properly. Most adults and many young children can use dry-powder inhalers, however, and beclomethasone dry powder for inhalation may therefore allow most asthmatic patients to benefit from inhaled corticosteroid treatment.

We designed a comparative study of the efficacy of beclomethasone dipropionate inhaled as a dry powder and as a conventional pressurised aerosol suspension.

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Patients and methods

Twenty adult outpatients with chronic asthma (11 men, 9 women; age range 30-65) who were receiving treatment with beclomethasone aerosol were selected. Each patient used a salbutamol aerosol on most days of the week to control mild symptoms, but none was receiving systemic corticosteroids. Before entry it was confirmed that the patients could use a conventional pressurised aerosol and the dry-powder inhaler (Rotahaler) efficiently. The study was a double-blind comparison of the following treatments, all patients receiving each treatment in random order for four-week periods: (1) placebo aerosol plus 100 μg beclomethasone dry powder four times daily; (2) placebo aerosol plus 150 μg beclomethasone dry powder four times daily; (3) 100 μg beclomethasone aerosol plus placebo dry powder four times daily. The dry-powder beclomethasone was inhaled from a capsule via a Rotahaler. The patients were asked to inhale one dose from the pressurised aerosol, then the contents of the capsule followed by a second dose from the aerosol on every occasion.

After the double-blind period of the study four weeks of placebo aerosol and placebo dry-powder treatment was given to all patients who had completed the active treatment months without developing an exacerbation of asthma severe enough to warrant treatment with prednisolone by mouth. Patients with exacerbations received prednisolone 20 mg/day for one week and subsequently active beclomethasone aerosol, and were temporarily withdrawn from the trial for four weeks. They were then re-entered in the next active treatment group. If deterioration occurred during the final four-week single-blind double-placebo section the patient was immediately withdrawn and appropriate treatment given.

All patients completed diary cards and assessed their overall asthma symptoms for each day and night by marking a 50-mm line marked "no symptoms" at one end and "severe symptoms" at the other. Also graded by the patients at the same times and by the same method were symptoms of breathlessness, wheeze, and cough. Peak expiratory flow rate (PEFR) was measured with a Wright's peak-flow meter and

recorded each day at 8 am and 8 pm. Also recorded on the diary cards were the numbers and times of use of salbutamol aerosol. Clinical assessments were made by the co-ordinator every two weeks, when measurements of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were made. Undesirable effects of treatment were judged by indirect questioning. Short tetracosactrin (Synacthen) tests were performed before entry and on the last day of each active treatment period.

Results

In the 60 active treatment periods there were seven exacerbations of asthma severe enough to warrant treatment with oral prednisolone. These seven treatment failures occurred in six patients—four during the low-dose (100 μg four times daily) dry-powder treatment and three during the active aerosol period. There were no treatment failures in the high-dose (150 μg four times daily) dry-powder period. The 14 patients who completed the double-blind section of the study without relapse were given double placebo treatment for four weeks, and nine of them deteriorated clinically during this time. Results were analysed using analysis of variance.

Salbutamol inhaler usage—There were no important differences between the active treatment groups. The mean number of puffs taken were 45·1, 45·3, and 43·2 (standard error of difference = 4·95) in the treatment groups 1, 2, and 3 respectively.

FEV_1 and FVC—The mean values for FEV_1 and FVC are shown in table I. At two weeks there were no important differences between the ventilatory function test results in any of the three groups, but at four weeks the 150-μg dry-powder results were slightly better than those recorded with the other two treatments.

TABLE I—*Mean values for FEV_1 and FVC at two weeks and at four weeks for the three treatment periods*

Treatment:		1	2	3	SE diff
Two weeks	FEV_1	1·83	1·94	1·87	0·1214
	FVC	2·93	3·03	2·92	0·1575
Four weeks	FEV_1	1·91	2·09	1·88	0·0842
	FEV	2·84	3·18	2·89	0·1383

SE diff = Standard error of difference.

PEFR—The means of morning and evening PEFR values were similar in the 150-μg dry-powder and 100-μg aerosol treatment groups, and these were higher than the mean values in the 100-μg dry-powder group. The morning mean PEFR during the 100-μg dry-powder treatment was lower than the mean values recorded during the other two treatments (table II).

TABLE II—*Morning and evening mean PEFR values for the three treatment periods*

Treatment:	1	2	3	SE diff
PEFR (morning) ..	245·5	257·3	259·4	5·89
PEFR (evening) ..	236·9	243·3	242·4	6·07

Patients' assessment of symptoms—Table III shows the mean scores for general symptoms, wheeze, breathlessness, and cough for the three treatment periods. These twice-daily assessments were analysed separately. The day symptoms scores show that the 150-μg dry-powder treatment was better than the smaller dry-powder dose in all scores except for cough. The aerosol was better than the 100-μg dry-powder treatment for cough and breathlessness. The night symptom scores showed no differences between the treatments, except for cough, when the aerosol was better than the 100-μg dry-powder.

Results of the short tetracosactrin tests showed that two patients had abnormal results on entry; in one, Addison's disease was diagnosed and subsequently confirmed by antibody studies, and the other, whose cortisol concentrations were abnormally high before and after the tetracosactrin test, was still undergoing investigations. Analysis of the results of the short tetracosactrin test (Friedman's rank test) showed no significant variations in the three treatment groups. No adverse reactions to any of the treatments were reported.

TABLE III—*Day and night mean symptom scores for the three treatment periods*

Treatment:	1	2	3	SE diff
Day				
Asthma symptoms ..	3·89	2·63	3·30	0·62
Wheeze	5·03	3·56	4·11	0·63
Dyspnoea	4·18	2·81	3·08	0·54
Cough	5·29	3·74	3·06	0·86
Night				
Asthma symptoms ..	3·28	2·49	3·02	0·58
Wheeze	4·34	3·41	3·54	0·53
Dyspnoea	3·92	2·46	2·62	0·78
Cough	4·89	3·61	2·56	1·04

Discussion

Our results showed that beclomethasone inhaled as a dry powder was as effective as the conventional pressurised aerosol in treating chronic asthma in the patients studied. There were few differences between the 100-μg dry-powder treatment and the conventional 100-μg aerosol, but most results favoured the aerosol, which was better in controlling cough. Inhalation of dry-powder beclomethasone probably did not cause cough, since a dry-powder lactose placebo was inhaled during the active aerosol treatment, and there was no important difference between the cough scores of the active aerosol and the 150-μg dry-powder treatment. Surprisingly, the larger dose of beclomethasone (600 μg daily) was slightly better than the conventional aerosol (400 μg daily) in terms of ventilatory function measured at the end of each active treatment period, but there were no important differences between these two treatments in any of the other parameters measured. Increasing the dosage of beclomethasone from 400 μg to 1600 μg by increments of 400 μg has previously been shown to result in no further therapeutic benefit.[2] No treatment caused significant changes in plasma cortisol concentrations before and after the tetracosactrin test.

The study was designed to ensure that patients were not taking conventional beclomethasone treatment unnecessarily. Six patients had exacerbations of asthma during the double-blind active period, and in nine of the remaining 14 asthmatic symptoms grew worse during the single-blind double-placebo period. Hence the asthmatic symptoms of most of the patients presumably justified treatment with beclomethasone by inhalation. The exacerbations of asthma were almost equally divided between the 100-μg dry-powder and 100-μg aerosol treatments, and no patient relapsed when receiving 150 μg dry-powder beclomethasone. We conclude that beclomethasone inhaled as a dry powder was an effective treatment for chronic asthma in our patients, and that 600 μg beclomethasone daily has advantages over the conventional aerosol treatment of 400 μg daily. This new method of administering beclomethasone should allow patients who cannot use a pressurised aerosol efficiently to benefit from inhaled corticosteroid treatment.

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