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Twice Daily Administration of Beclomethasone Dipropionate Dry-Powder in the Management of Chronic Asthma

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SUMMARY **In a double-blind cross-over study beclomethasone dipropionate inhaled as a dry-powder in a dose of 400 μg twice daily was compared with a conventional aerosol in a dose of 100 μg four times daily in 16 outpatients with chronic asthma. Each of the 2 treatments lasted for 4 weeks. There was no significant difference with respect to daily peak expiratory flow rates, symptom scores, bronchodilator usages and other lung function measurements between the 2 treatments. Tetracosactrin tests were within normal limits and no clinical oral candidiasis was observed throughout the study. In conclusion, beclomethasone dipropionate dry-power given twice daily was effective for the control of asthma and could be recommended for patients with poor drug compliance.**

Inhalation of topically active beclomethasone dipropionate (BDP) for the treatment of asthma has been available for over 10 years and has been shown to be both effective and safe.[1] BDP is normally given in the form of metered dose aerosol. For those who have difficulty in synchronising the inhalation of aerosol with the actuation of an inhaler (*e.g.*, children or the elderly), an alternative dry-powder inhaler is available. This contains BDP as a microfine powder in an inert lactose base within a gelatin capsule. The capsule is separated into 2 halves by rotating the device (called a Rotahaler), and the contents are inhaled using a breath activated mechanism. The drug is released even at very low inspiratory flow rates. The BDP Rotahaler (400-800 μg/day) has been shown to be as effective as the conventional metered dose inhaler (400 μg/day).[2-5] The usual recommended dose from a BDP Rotahaler is 200 μg four times daily. The dose frequency is partly due to convention, and partly due to rapid metabolism of inhaled BDP.[6] Recently a BDP aerosol given twice daily was found to be effective in the control of asthma.[7] The British National Formulary then suggested that a BDP Rotahaler could also be used twice daily.[8] However, as far as we are aware, the efficacy of a BDP Rotahaler using this dosing frequency has never been reported. This has prompted us to conduct a trial to determine whether the twice daily use of a BDP Rotahaler would be as effective as the four times daily use of a metered dose inhaler in improving patient compliance.

MATERIALS AND METHODS

A four-week double-blind cross-over study was done to compare the effect of a BDP aerosol with a BDP rotacap. Adult asthmatics, older than 15 years of age who were receiving 400 μg daily of BDP from an inhaler, who demonstrated at least 15% reversibility in lung function 15 min after inhaling 2.5 mg neubilised salbutamol and who had not received oral steroids in the previous 4 weeks, were chosen for the study. Patients were given the following 2 regimens in random order for 4 weeks each, after a 2-week run-in period. The regimens were (a) a pressurised BDP aerosol and placebo rotacap and (b) a pressurised placebo aerosol and BDP rotacap. The required dose was 2

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puffs of aerosol 4 times daily and 2 rotacaps twice daily. Patients were asked to complete daily record cards to assess symptoms and record peak expiratory flow rate measurements. Symptom scores of night disturbance, wheeze and activity restriction, were recorded on a scale of 0 for no symptoms to 3 for severe symptoms while cough and sputum production were recorded on a scale of 0 (no symptoms) to 2 (severe symptoms). Three forced expiratory peak flow measurements were obtained with a mini-Wright peak flow meter on waking and at bed time; the highest value was recorded on each occasion.

Clinical assessments included a swab examination of the mouth and the throat for candidiasis, a short tetracosactrin test (250 μg ACTH intravenously) and lung function measurements. The lung function measurements including forced expiratory volume in 1 sec (FEV_1), forced vital capacity (FVC) and peak flow rate (PFR) were performed using a digital pneumotachograph (Hewlett Packard 47401A). These assessments were made at the start of the 4-week study and at weekly intervals thereafter. Patient preferences for treatment devices and treatment periods were obtained at the end of the study.

Only the last 2 weeks of each treatment period were analysed to minimise any " carry over " effects. Comparisons of lung function between the 2 treatment periods were made using paired *t* tests. Symptom scores were compared using Wilcoxon's matched pairs signed-ranks tests.

RESULTS

Patient characteristics are shown in Table 1. Nine patients received the pressurised aerosol and 7 the Rotahaler during the first period and *vice versa* during the second period. The lung function measurements for both groups were very similar at the start of the study, indicating that the 2 groups were comparable. As no other effects were seen, the data for each Rotahaler period and each aerosol period were combined.

Symptom scores and daily bronchodilator usage

The mean daily scores for night symptoms, wheeze, activity restriction, cough and sputum production were similar for both treatment regimens. The mean total daily score for all the symptoms was relatively low, indicating asthma was well controlled. The overall bronchodilator usage was almost identical in both groups (Table 2).

Lung function tests

The mean morning and evening PFR measurements during the last 2 weeks of each treatment were slightly higher during the rotacap period but the difference was not significant ($p > 0.05$). The lung function measurments, FEV_1 and FVC, performed during clinic visits at the end of each treatment period, before and after inhalation of 2.5 mg nebulised salbutamol, were almost identical for both devices (Table 3).

Treatment preferences

At the end of the study, a physician's assessment of the control of symptoms during each period indicated that there was no difference between treatments for eight of the patients. For the other eight, control was better for four patients in the aerosol period and four in the rotacap period. When the 16 patients were asked to state their preference for a device and for the treatment period based on control of symptoms, five preferred the aerosol period, nine the rotacap period and two had no preference. Seven patients preferred using the metered dose inhaler and three the Rotahaler. Six had no preference.

Side effects

There was no clinical evidence of candidiasis of the throat and the mouth throughout the study period.

All the serum cortisol levels were within the normal range both pre- and post-tetracosactrin stimulation, indicating no evidence of adrenal suppression (Table 4).

One patient complained of throat irritation thought to be due to aerosol application. No other side effects or adverse events were recorded.

DISCUSSION

Our results showed that BDP given only twice daily in the form of dry-powder was as effective as the conventional aerosol given 4 times daily in the treatment of chronic asthma. This dose frequency would be more acceptable to patients, as it would certainly improve drug compliance which is a major problem with prophylactic inhaler therapy.[9] Although a single daily dose regimen of systemic steroid is as effective as divided daily doses in controlling various inflammatory diseases,[10] once daily inhaled corticosteroid is found to be ineffective in chronic asthma.[11]

As the Rotahaler needs to be refilled with a capsule each time it is used, it appears that it is more convenient to use the metered dose inhaler. However, 9 of our 16 patients found the Rotahaler acceptable. The loading procedure would in theory prevent excessive use of

Table 1 Characteristics of patients

	No. of patients	Mean	Range
Male	6		
Female	10		
Age (years)		36.7	15-54
Duration of asthma (years)		12	3-34
Extrinsic asthma	12		
Intrinsic asthma	4		
B2 agonist (inhaled)	16		
B2 agonist (oral)	9		
Theophylline	15		

Table 2 Mean daily symptom score and inhaled bronchodilator usage

	Dry-powder	Aerosol
Night symptoms	0.27 ± 0.53	0.28±0.52
Wheeze	0.45± 0.55	0.46±0.53
Activity restriction	0.55± 0.79	0.56±0.77
Cough	0.42± 0.46	0.36±0.45
Phlegm	0.76± 0.62	0.64±0.62
Bronchodilator usage (puffs)	7.70± 2.60	7.50±2.20

Wilcoxon's test showed no significant difference between the two groups.

Table 3 Lung function tests

	Dry-powder	Aerosol
Daily at home		
Waking PEF (1/min)	311±103	294±105
Evening PEF (1/min)	324±105	310±100
At clinic visits		
FEV 1 (1.) pre-salbutamol	2.0±0.76	2.0±0.72
FEV 1 (1.) post-salbutamol	2.2±0.77	2.2±0.76
FVC (1.) pre-salbutamol	2.8±0.85	2.8±0.60
FVC (1.) post-salbutamol	3.4±0.68	3.3±0.82

Students'*t* test showed no significant difference between the two groups.

Table 4 Mean plasma cortisol levels pre and post ACTH stimulation (nmol/l)

	Dry-powder			Aerosol		
	Pre	Post	Increment	Pre	Post	Increment
Mean	376	600	224	400	642	242
SD	136	129	118	196	230	113

the inhaler, and the absence of fluorocarbon propellant in the Rotahaler would also be an advantage where there was fear of propellant toxicity. More importantly, the use of Rotahaler would help to overcome the problem of poor drug compliance and possibly also the problem of nonsynchronisation seen with the use of conventional metered dose inhalers.

Despite the high dose of BDP dry-powder, there was no evidence of adrenal suppression or increased incidence of oral candidiasis.

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