THE EFFICACY OF HIGH DOSE INHALED BUDESONIDE IN REPLACING ORAL CORTICOSTEROID IN ASIAN PATIENTS WITH CHRONIC ASTHMA

W C Tan, T B Chan, T K Lim, E C K Wong

ABSTRACT

We studied 22 Asian patients with steroid dependent asthma. Using a clinical approach to the addition of high dose inhaled budesonide and tapering of systematic steroid, we were able to substitute 5 to 20 mg prednisolone with 800 µg per day of inhaled budesonide in all patients. There was also a greater reduction in nocturnal symptoms and awakenings and a smaller overnight fall in PEFR during treatment with budesonide than with prednisolone. Inhaled budesonide was an effective long term substitute for prenisolone in chronic asthma.

Keywords: Chronic asthma, Inhaled steroid, Nocturnal asthma, budesonide, prednisolone.

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INTRODUCTION

Inhaled corticosteroids are commonly used to supplement and sometimes to replace systemic corticosteroids in the management of patients with chronic asthma (1-7). Complete replacement with low dose inhaled corticosteroids is often not achieved in many patients (1-3) though this is improved when higher doses of inhaled corticosteroids are used (2, 3, 5). Beclomethasone dipropionate has been extensively studied in this way (1-6, 8-12). Similar results have been reported in a few recent studies on the newer inhaled steroid budesonide (13-16). The usefulness of high dose inhaled steroid has not been stidued in Asian patients. The aim of this study was to examine prospectively the long term efficacy of twice daily inhaled budesonide in replacing oral steroids in Asian patients with moderate to severe chronic asthma, using an experimental protocol than can be easily applied in clinical practice.

Department of Medicine
National University Hospital
Lower Kent Ridge Road
Singapore 0511

W C Tan, MBBS, MRCP (UK), FRACP, AM (S'pore), FRCP (Edin)
Associate Professor

T B Chan, MBBS, M Med (Int Med) (S'pore), AM (S'pore)
Senior Lecturer

T K Lim, MBBS (Mal), M Med (Int Med) (S'pore)
Senior Lecturer

Astra Asia Regional Office, Singapore

E C K Wong, PhD
Clinical Research Manager

PATIENTS AND METHODS

Twenty-five patients, 16 women and 9 men, mean age 43 ± 10 (mean ± 1SD) years (range 28-58 years) with chronic stable steroids-dependent asthma were recruited from the outpatient clinic of the National University Hospital of Singapore. These patients had been treated with daily prednisolone for at least 6 months before the study because they had required more than three 2-week courses of systemic corticosteroid in the preceding six months or attempts to discontinue prednisolone had resulted in a marked exacerbation of asthmatic symptoms. Twenty-two patients completed the study and this group is more fully characterised in Table I. The dosages of the oral bronchodilators were kept unchanged throughout the study, but the frequency of administration of inhaled bronchodilators was varied to control symptoms.

The study was of an open design and consisted of three phases (Fig 1). The first phase consisted of a two week run-in period during which the patients continued to take the maintenance dose of prednisolone. Baseline spirometric measurements of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), the peak expiratory flow rate (PEFR) were made. In the second phase, patients received the maximum daily dose of inhaled budesonide (Pulmicort®, Astra Sweden), 1600 µg delivered via a spacer device in 4 metered doses twice daily while the dose of prednisolone was reduced by 1 mg every two weeks until it was withdrawn altogether or reduced to the lowest possible dose without provoking a relapse of symptoms or a greater than 20% fall in the FEV_1. In the last phase the dose of budesonide was similarly decreased by 200 µg every two weeks to a minimum of 800 µg a day. Throughout the study the patients were assessed clinically and spirometric measurements made every two weeks. The patients also kept diary card records of 1) symptoms scored from 0 to 3 (none to severe), comprising quality of sleep, day time

Table I
Characteristics of 22 Steroid-dependent asthmatic patients before starting prednisolone

Parameters	Mean ± 1s.d.	Characteristics	No. of Patients
Age (yrs)	42.5 ± 9.2	Male	9
Years of Asthma	15.9 ± 9.0	Female	13
Blood Eosinophil (per cu mm)	180(17 to 900)†	Positive skin prick tests	16
PEFR (% pred. Normal)	51.4 ± 18.5	Daily steroids	22
Diurnal Variation** in PEFR (%)	30(14 to 517)†	Smoking History	0
Prednisolone (mg/day)	11.7 ± 4.8	Chronic bronchitis	0
Steroid reversibility* (% change in FEV_1)	48.6 ± 19.1	Bronchodilators	
		Theophylline	22
		β_2 agonist (tab)	12
		β_2 agonist (inhaler)	22

** $\frac{\text{PEFR at bedtime} - \text{PEFR on awakening}}{\text{PEFR at bedtime}}$

* After 2 weeks of prednisolone, 30mg per day.

† median (range)

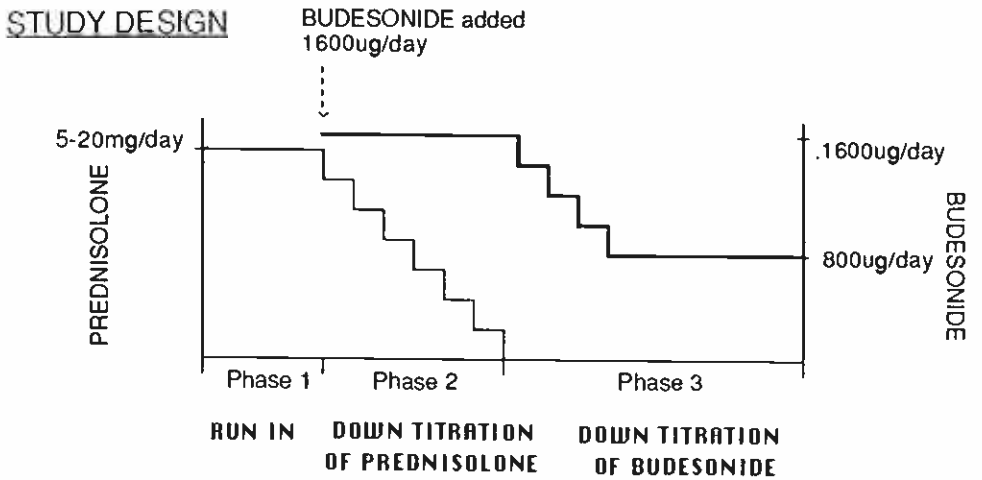

Fig 1
Study design consisted of 3 phases: Run in; down titration of prednisolone; down titration of budesonide.

activity, day wheeze and cough; 2) PEFR before sleep and on awakening in the morning; 3) the frequency and the amount of inhaled bronchodilator used. Throat swabs for the culture of Candida albicans and venous blood samples for eosinophil counts were taken at the beginning and at the end of the study. Spirometry was performed by standard techniques (17) using a dry rolling spirometer (Gould USA). A count of tablets and a check of inhaler technique were made at each clinic visit. Informed written consent was obtained from all the patients.

ANALYSIS OF RESULTS

The data from the clinic visits and the diary cards were analysed. All data were expressed as mean ± 1s.d. The results of treatment with prednisolone and with budesonide were compared by analysing respectively the data of: (1) the run-in period of 18 ± 9 days (ii) the period at the end of the study when the patients were receiving the lowest final dose of budesonide 76 ± 33 days. The parametric data during the periods of treatment with prednisolone and with budesonide were analysed by Student's t-test and by ANOVA methods. Pulmonary function measurements showing a skewed distribution and non parametric data from diary cards were analysed by the Wilcoxon matched pairs signed rank test. Significance was assumed at $p < 0.05$.

RESULTS

Twenty-two patients completed the study. Three patients were withdrawn from the study: one due to poor compliance with the experimental protocol, one to an acute infective exacerbation of asthma and one to transient hoarseness of voice.

The pre-study minimum maintenance dose of prednisolone was 11.7 ± 4.8 mg (range 5 to 20 mg). This dose was inversely correlated with the baseline PEFR before treatment with prednisolone. $Y = -0.1888x + 22.16$ $R = 0.75$, $p < 0.0004$. There was no correlation between the diurnal variation in PEFR and the pre-study maintenance dose of prednisolone but the variation was positively correlated with the magnitude of steroid reversibility $y = 0.082x + 43.70$, $R = 0.55$, $p < 0.04$. Discontinuation of prednisolone was attained in all patients in 12 ± 10 (mean ± SD) weeks (range 1 to 36). The dose of budesonide was reduced to the lowest maintenance dose over a period of 5.1 ± 1.8 weeks (range 3 to 8 weeks). This final daily dose of budesonide was 800 µg in 21 out of 22 patients and 1600 µg in 1 patient. The total period of the study was 38 ± 8.4 weeks (range 28 to 62 weeks).

CLINIC ASSESSMENT

Measurements of PEFR made at the same time of the day at each clinic visit showed that the mean PEFR during the treatment with 800 µg budesonide, was 80.75 ± 20.12 (% predicted normal) which was significantly higher than that during the treatment with prednisolone, 70.17 ± 20.90 ($p < 0.01$). The FEV_1 72.14 ± 20.30 (% predicted normal), FVC 85.40 ± 16.67 (% predicted), during treatment with budesonide were higher compared with FEV_1 67.32 ± 23.59, FVC 81.68 + 19.57, during prednisolone but did not reach statistical significance.

DIARY CARD DATA

Diary card data of the mean symptoms scores for daytime activity, cough, wheeze and nocturnal symptoms were significantly lower during treatment with budesonide than that during treatment with prednisolone ($p < 0.001$), but the daily doses of inhaled bronchodilators during the two periods were not different (Table II). The PEFR at bedtime (PM PEFR) and on awakening in the morning (AM PEFR) during budesonide treatment were significantly higher than the PM PEFR and AM PEFR during treatment with prednisolone. The diurnal variation in PEFR (overnight fall %) on budesonide was smaller than that on prednisolone (Table II).

No patient had clinical oral candidiasis. Candida albicans was cultured from the throat swabs of 17 patients during both treatment periods, five patients during treatment with prednisolone only, and two patients during treatment with budesonide only. The blood eosinophil count was higher during treatment with budesonide compared with that during prednisolone (Table II).

There was no difference between the sexes in all the above parameters determined from the clinical assessment and diary card data. All p values were >0.1.

DISCUSSION

Although previous studies have shown efficacy and safety of high dose inhaled steroid in Caucasian patients there

Table II

Comparison of the diary card symptom score, use of inhaled β agonist, PEFR and blood eosinophils during treatment with prednisolone & with budesonide in 22 steroid dependent asthmatic subjects.

	Treatment Periods		
	Prednisolone	**Budesonide**	**p-value**
Daily Symptom Score (Scale 0-3)			
Activity	0.07(0 to 1.0)	0(0 to 1.0)	<0.001
Cough	0.03(0 to 1.15)	0.02(0 to .32)	<0.001
Wheeze	0.35(0 to 1.26)	0(0 to .61)	<0.001
Sleep Quality	0.44(0 to 1.08)	0(0 to 0.88)	<0.001
Daily Usage of Inhaled β_2 agonist (No. of puffs)	6(0 to 14)	4(0 to 11)	NS
PEFR (L/min)			
Bed time	346 ± 32†	385 ± 28†	<0.02
Morning awakening	307 ± 40†	378 ± 25†	<0.001
Overnight fall (%)	8.77(-26 to 42)	.38(-4 to 18)	<0.05
Blood Eosinophils (per litre)	0.18(.02 to .90) x 10^{-9}	0.44(.09 to .96) x 10^{-9}	<0.05

† mean ±s.d. All other values are in median(range)

has been no such study in Asian patients. In this study inhaled budesonide 800 µg per day was an effective and well tolerated substitute for 5 to 20 mg (mean 11.7 mg) of prednisolone in all steroid-dependent patients with chronic asthma. Asthmatic symptoms and nocturnal falls in PEFR were further reduced by budesonide. These results in Asian patients compared favourably with the results of other studies (1) (3-6)(8-9). Adelroth et al (13) found that a minimum daily dose of 800 µg to 1600 µg of budesonide was required as replacement for a daily dose of 5 to 20 mg (mean 8.7 mg) of prednisolone in 18 of 38 (47%) steroid-dependent asthmatic patients. Similarly, Laursen et al (14) reported a successful replacement with 1600 µg of budesonide in 40% of his patients who had been treated with 13.9 mg prednisolone daily. Smith and Hodson (4) found that 500 to 2000 µg/day of beclomethasone dipropionate enabled the complete withdrawal of oral corticosteroids in a patient requiring 5 mg or less of prednisolone and a reduction in dosage in patients receiving 15 mg daily. Toogood et al studied 34 steroid-dependent asthmatic patients for 80 weeks and succeeded in substituting oral prednisolone 12.2 ± 0.8 mg (mean ± 1sem) in 15 patients with 1200 µg beclomethasone per day (6). Hence, most studies had shown that inhaled corticosteroid even at high dosages was at best just as effective as oral prednisolone. This study further showed that high dose inhaled corticosteroid administered through a spacer could be more effective than moderate doses of oral prednisolone in steroid responsive asthmatic patients.

There are several possible explanations for the uniform efficacy of budesonide in our study. First, in an open study, it might be argued that improvement with budesonide might have been due to a placebo effect in some instances. We felt this was unlikely in our patients who preferred oral medications and had required regular doses of oral corticosteroids to control their asthmatic symptoms before this study. The study design was open, similar to that employed by Adelroth et al (13), and Toogood et al (6) so that initial treatment could be maximised followed by a gradual and graded reduction of first oral and then inhaled steroid without provoking a severe exacerbation of asthmatic symptoms in the patients. The second reason could be that our patients had milder asthma compared with those studied by other workers. We felt that this was unlikely for the following reasons: (i) the minimum maintenance doses of prednisolone before the study were at least as much or greater than that reported in other studies (13, 14) (ii) the final maintenance doses of prednisolone were related to the severity of airflow obstruction prior to treatment with oral prednisolone, and (iii) patients had large diurnal variations in PEFR before treatment with prednisolone.

The findings that when patients were treated with budesonide (800 µg daily), they showed a greater reduction in nocturnal symptoms and awakenings, and a smaller overnight fall in PEFR than when they were treated with prednisolone, suggested that inhaled budesonide may be effective in the treatment of nocturnal asthma. Several studies have indicated that corticosteroids helped control nocturnal asthma as evidenced by an improvement in mean PEFR and a reduction in the magnitude of its circadian variation (18-20). Laursen et al achieved similar improvements of the morning and evening PEFR in their patients but with twice the dose of budesonide given together with a minimum maintenance dose of prednisolone (14). There is some evidence to suggest the nocturnal asthma may be the clinical manifestation of the late asthmatic response (LAR) to inhaled allergens (21-23). Since corticosteroids can inhibit the LAR (24-27), it is possible that corticosteroids improve the control of nocturnal asthma by modifying the LAR, although this has not been proven.

We speculate on the reasons for the apparent slight but distinct superiority of inhaled budesonide over oral prednisolone in the control of nocturnal asthma in this study. Firstly, it is conceivable that our patients were inadequately treated with oral prednisolone at the start of the study and that the improvement with budesonide was a result of a greater overall efficacy of this medication over 5 to 20 mg of prednisolone. Secondly, the topical inhibitory effect could be greater than the systemic effect.

Side effects in this study were uncommon. The only adverse effect noted during this study was hoarseness of voice in one patient in the absence of clinical oral candidiasis (28). Normal phonation returned three weeks after withdrawal from the study (29). We did not find systemic withdrawal symptoms such as an exacerbation of allergic symptoms or myalgia noted in other studies in which inhaled steroid was substituted for oral steroid (30).

In conclusion, we have shown that an intermediate dose of inhaled budesonide could be an effective long term substitute for oral steroid in Asian patients with moderate to severe steroid-dependent chronic asthma. Our data suggested that budesonide might be slightly more effective than prednisolone in the treatment of nocturnal asthma. However in view of the small sample size and the large variation displayed by some of the study variables further studies might be necessary to confirm the findings in this study.

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