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Long term clinical comparison of single versus twice daily administration of inhaled budesonide in moderate asthma

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Abstract

***Background* – Inhaled steroids are widely used in the treatment of mild to moderate asthma. However, long term compliance with inhaled steroids is poor and administration of a single daily dose may improve compliance.**

***Methods* – A double blind, randomised study was performed to determine whether inhaled steroids given once daily at bedtime are as efficacious as a twice daily regimen in the long term maintenance of moderate asthmatic patients. Forty adults of mean age 37 years with moderate asthma (mean (SE) forced expiratory volume in one second (FEV_1) 73·6 (1·4)% predicted, mean morning peak expiratory flow (PEF) 328 l/min) were randomised to receive either a twice daily dose (400 µg morning and bedtime) of inhaled budesonide (group A) or a once daily dose of 800 µg (group B) and were followed for a period of 12 months. Asthma symptom scores (assessed according to a modified Borg scale), inhaled β_2 agonist consumption, and peak expiratory flow rates were recorded daily. Spirometry and airways responsiveness to methacholine (PC_{20}) were measured at the end of each period of three months of treatment.**

***Results* – There was no difference between the two groups at baseline and during the follow up period in the PC_{20} for methacholine. However, a difference was seen between the two groups in the mean daily number of β_2 agonist inhalations (1·4 (0·1) puffs/patient/day in group A *v* 2·3 (0·1) in group B), the PEF variability (episodes of decrease in PEF of >20%) (0·22 (0·01) episodes/patient/day in group A *v* 0·40 (0·02) in group B), and for asthma symptom scores (0·30 (0·04) in group A *v* 0·42 (0·06) in group B) for the 12 month period of the study.**

***Conclusions* – Although both regimens provide good clinical control, twice daily doses of 400 µg inhaled budesonide are more effective than a single dose of 800 µg at bedtime in the long term control of stable moderate asthma.**

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Keywords: inhaled budesonide, asthma.

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Inhaled steroids are potent bronchial anti-inflammatory agents[1 2] and are widely used in the treatment of asthma. Initially they were given four times daily,[3] but it has since been shown that twice daily regimens may be as effective as administration four times daily.[4–6] However, long term compliance with inhaled steroids is poor[7] and, if extrapolation from oral compliance studies can be made,[8] the decrease of inhalation frequency to once daily may improve compliance. Comparisons of the efficacy of once and twice daily administration have given conflicting results. Two studies have shown that administration of inhaled steroids twice daily provides better control of asthma than a once daily regimen,[9 10] while in two other studies[11 12] the reduction of frequency of budesonide inhalations to only once daily was not associated with decreased efficacy. However, a potential problem in the interpretation of these results is the relatively short duration of follow up in these clinical trials (3–4 weeks).

A double blind, randomised study was performed to determine whether inhaled steroids given once daily at bedtime are as efficacious as a twice daily regimen in the long term maintenance of moderate asthmatic patients.

Methods

PATIENTS

Forty adults of mean age 37 years (range 19–66) with moderate asthma (according to the International Consensus Report on the Diagnosis and Management of Asthma[13]) were recruited. The baseline characteristics of the subjects are summarised in the table. All subjects were on a daily dose of either 1000 µg (500 µg twice daily) of inhaled beclomethasone dipropionate (eight in group A and nine in group B), or 800 µg (400 µg twice daily) of budesonide (two and one, respectively), and used a β_2 agonist on demand to control asthma symptoms. Four patients used long acting theophylline and serum levels were measured before and every three months during the study, and were kept within normal values. The patients were observed during a run-in period of four weeks and were included in the study only if their asthma was stable.

The protocol of the study was accepted by the local ethics committee and all subjects gave informed consent.

DESIGN OF STUDY

The patients were randomised to receive either a twice daily dose (400 µg morning and bedtime) of inhaled budesonide (group A) or a

Mean (SE) characteristics of asthmatic patients included in the study

	Group A	*Group B*
No. of subjects	20 (11 M; 9 F)	20 (11 M; 9 F)
Age (years)	35 (2·2)	39 (2·4)
Duration of asthma (years)	9·1 (0·9)	10·3 (1·0)
No. with treatment		
β_2 agonists	20	20
Puffs per day	1·7 (0·1)	1·5 (0·1)
Theophylline	1	3
Inhaled steroids	20	20
Duration of treatment (months)	7·0 (6·2)	5·1 (5·6)
FEV_1 (% predicted)	72·8 (1·4)	74·4 (1·5)
PEFR (l/min)		
Morning	334 (12)	322 (11)
Evening	342 (13)	336 (13)
PC_{20} methacholine (mg/ml)	1·60 (0·2)	1·66 (0·2)

FEV_1 = forced expiratory volume in one second; PEFR = peak expiratory flow rate; PC_{20} = provocative concentration causing a 20% fall in FEV_1.

once daily dose of 800 µg at bedtime (group B) and were followed for a period of 12 months. Both placebo and active (200 µg budesonide per puff) aerosols were generated from metered dose inhalers and delivered via a spacer (Aerochamber). To maintain blindness each patient received four identical metered dose inhalers that were numbered. Two (nos 1 and 3) contained the active drug and two (nos 2 and 4) contained placebo. Both patients and investigators were blinded to the content of the inhalers. Patients in group A were instructed to inhale two puffs from inhaler no. 1 and two puffs from inhaler no. 2 in the morning and two puffs from inhalers nos 3 and 4 at bedtime, while patients in group B were instructed to inhale two puffs from inhalers nos 2 and 4 in the morning and two puffs from inhalers nos 1 and 3 at bedtime.

SYMPTOMS

The patients kept a diary and recorded scores for daytime and night time asthma symptoms (cough, chest tightness, sputum, wheezing, and dyspnoea) which were graded on a modified Borg scale from 0 to 10.[14] Inhaled β_2 agonist consumption was also recorded daily.

PULMONARY FUNCTION TESTS

Peak expiratory flow rates were measured in the morning and at bedtime and before β_2 agonist use using a mini-Wright peak flowmeter. Spirometric values (Compact, Vitalograph) and airways responsiveness to methacholine were measured at the end of each three month period of treatment.

Responsiveness to methacholine was measured according to the technique described by Juniper *et al*[15] and the results are presented as geometric means. The provocative concentration of methacholine causing a 20% fall in FEV_1 (PC_{20}) was determined by interpolating the last two points of the dose response curve on a semilogarithmic scale.

DATA ANALYSIS

Comparisons of lung function and airways responsiveness to methacholine between the two groups and the effect of the treatment on these parameters were carried out using the two way repeated measures analysis of variance (ANOVA). When the overall ANOVA was significant, post hoc comparisons were made. χ^2 (degree of freedom 1) statistics were used to compare changes in asthma symptoms, inhaled β_2 agonist consumption, and the variability in peak expiratory flow (PEF) (episodes of decrease in PEF >20%).

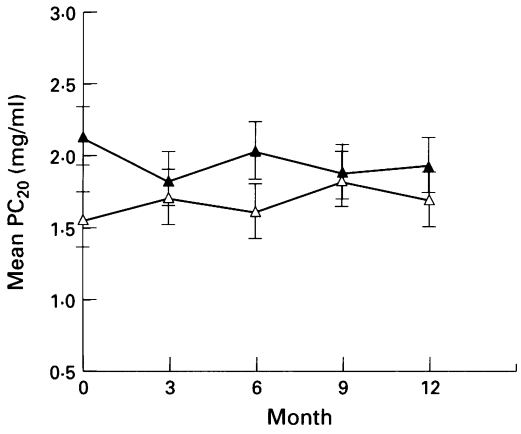

Figure 1 Mean PC_{20} for methacholine before entering the study and every three months of the 12 month follow up period (△ = group A, ▲ = group B).

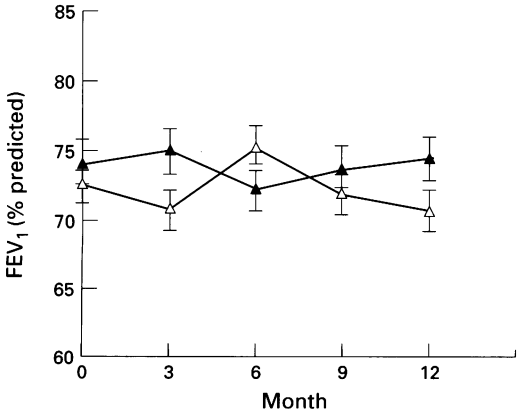

Figure 2 Mean FEV_1 before entering the study and every three months of the 12 month follow up period (△ = group A, ▲ = group B).

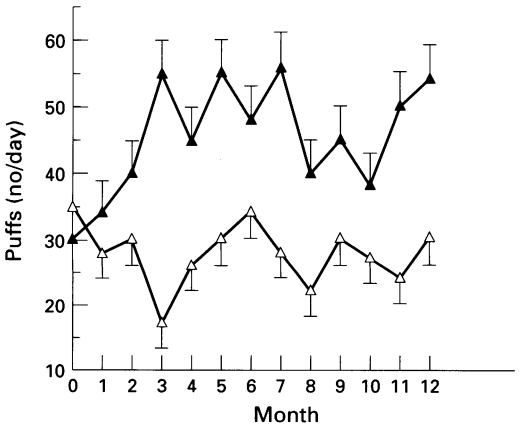

Figure 3 Mean inhaled β_2 agonist consumption before and during the 12 month follow up period △ = group A, ▲ = group B.

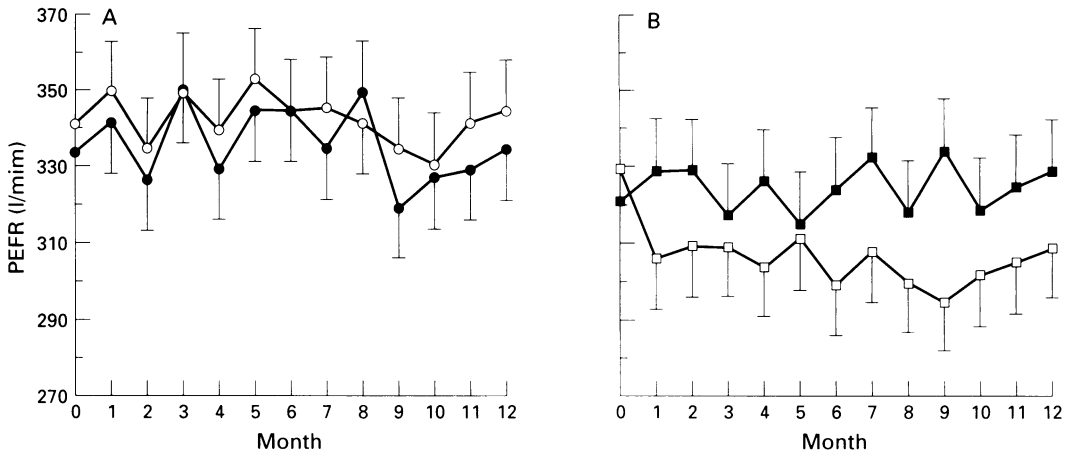

Figure 4 Mean PEFR values for (A) group A in the morning (●) and evening (○), and (B) for group B in the morning (■) and evening (□) during the 12 month follow up period.

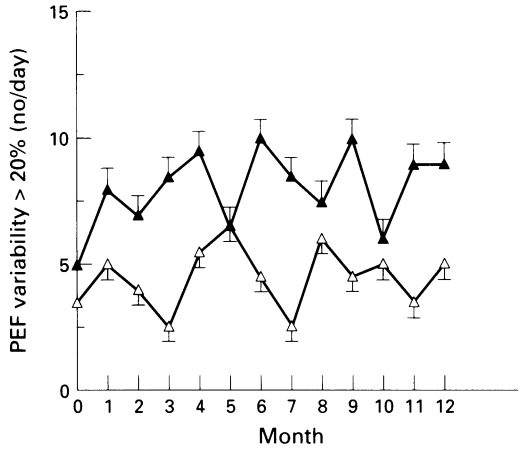

Figure 5 Mean number of episodes of a decrease in PEF of >20% before and during the 12 month follow up period. △=group A; ▲=group B.

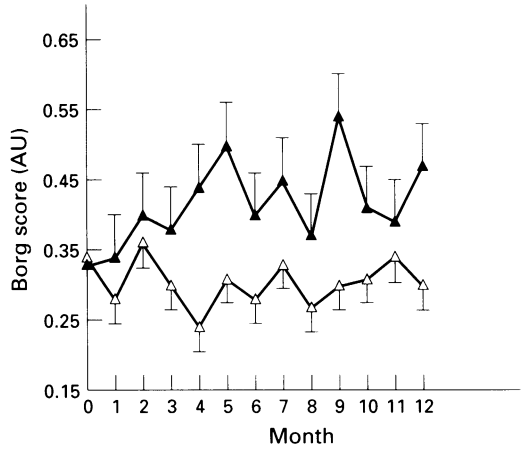

Figure 6 Mean symptom scores before and during the 12 month follow up period. △=group A; ▲=group B.

Results

Forty adults with moderate asthma were recruited to the study. Four patients had to be withdrawn (two in each group) because of lack of compliance in recording data. The final analysis therefore includes 36 patients who completed the study. No patient required oral prednisolone during the study.

There was no significant difference between the two groups at baseline in the PC_{20} for methacholine (1·56 mg/ml for group A and 2·16 mg/ml for group B) or in FEV_1 (72·8 (1·4)% and 74·4 (1·5)%, respectively). The PC_{20} for methacholine and spirometric parameters were also measured at the end of each three month period. No significant changes were found among and between the two groups in either the PC_{20} for methacholine (fig 1) or in the FEV_1 (fig 2).

However, as shown in fig 3, there was a significant difference between the two groups for the mean daily number of β_2 agonist inhalations (1·4 (0·1) puffs/patient/day in group A compared with 2·3 (0·1) in group B, $p<0·001$).

The mean morning and evening values of PEFR did not change significantly throughout the study in group A, and diurnal fluctuations were minimal (fig 4). In group B morning PEFR values remained stable, but evening PEFR values decreased following the first month of treatment and diurnal variation was more significant. There was also a significant difference between the two groups for the PEF variability (episodes of decrease in PEF >20% in relation to morning values). The mean number of episodes/patient/day was 0·22 (0·01) in group A and 0·40 (0·02) in group B ($p<0·001$), indicating better asthma control in group A (fig 5).

Asthma symptom scores remained minimal in group A during the whole follow up period (0·30 (0·04) on a scale of 0–10). This was significantly better than the scores in group B (0·42 (0·06), $p<0·005$) (fig 6).

Discussion

This study shows that, in patients with moderate asthma a twice daily dose of inhaled budesonide provides better long term control of asthma than a single dose at bedtime. This is in contrast with two previous studies, one with budesonide[11] and one with beclomethasone dipropionate,[12] in which a single daily dose of inhaled steroid did not give significantly different results from a twice daily regimen. However, both studies were of short duration (three and four weeks), a period that usually is not sufficient to determine whether symptoms are controlled in subjects with mod-

erate asthma. Two previous studies have shown that once daily administration of beclomethasone is less effective than twice daily treatment.[9 10] These studies were criticised[12] because patients with severe asthma were included, or because the single dose regimen was given in the morning while asthma symptoms and airways inflammation are worse at night and steroids seem to be more effective when given in the evening.[16] In our study, however, only patients with moderate asthma were included, they were followed for a long period, and the once daily regimen was given at bedtime. Nevertheless, the mean daily number of β_2 agonist inhalations, asthma symptoms, and the number of episodes of a decrease in PEF of >20% were all increased when inhaled steroids were reduced to a single daily dose. However, from a clinical point of view both groups showed good control of asthma symptoms (symptom score 0·3 and 0·42, respectively). Although there was a significant difference between the two modes of treatment in controlling asthma symptoms, the mean PC_{20} and FEV_1 were not significantly different between the two groups. Progressive withdrawal of steroids may cause an increase in bronchial hyperresponsiveness,[17] although Haahtela and coworkers[18] recently reported that, following two years of inhaled steroid treatment, bronchial hyperresponsiveness was maintained in 74% of the patients even when inhaled budesonide was reduced from 800 μg/day to 400 μg/day.

It has been suggested that a single daily dose may reduce side effects of inhaled steroids. However, Gagnon and associates[12] have shown that cortisol levels and the response to ACTH remained normal, and the incidence of dysphonia and oral candidiasis was the same, for the different modes of administration. The only advantage of a single daily dose of inhaled steroids would therefore be convenience for the patient. We consider that a single daily dose of inhaled budesonide may provide good asthma control in very stable patients for a limited period of time. However, for patients with worsening episodes of asthma and/or for long term control the potential benefits of a better compliance with a single daily treatment may be overshadowed by the less effective control of asthma symptoms. Finally, our results apply for inhaled budesonide only. These results may not predict results with other inhaled steroids with different affinity for glucocorticoid receptors, systemic bioavailability, and lipophilicity.

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