

Use of inhaled corticosteroids in patients with mild asthma

Sture Lorentzson, Jacob Boe, Göran Eriksson, Gunnar Persson

Abstract

A double blind, parallel group study was carried out to investigate the effect of inhaled budesonide in a moderate (200 µg) and a low (100 µg) twice daily dosage compared with the effect of placebo in 103 adults with mild symptomatic asthma. Subjects recorded peak expiratory flow (PEF), asthma symptoms, and beta₂ agonist consumption at home for a period of seven weeks (a one week run in and six weeks' treatment). Morning baseline PEF (around 80% of predicted normal) increased non-significantly to 88% with 200 µg budesonide daily and to 90% ($p < 0.05$) with 400 µg, compared with 81% with placebo. Evening PEF (around 94% of predicted normal) did not change significantly with active or placebo treatment. By comparison with placebo, there was a significant decrease in nocturnal asthma symptoms and beta₂ agonist consumption. The changes during the day were less pronounced and significant only for 400 µg budesonide daily. No significant differences between the two active treatments were detected. It is concluded that low doses of inhaled budesonide are effective in patients with mild symptomatic asthma, particularly for night time symptoms and early morning lung function. The early introduction of inhaled corticosteroids for patients with mild asthma and night time symptoms may improve their quality of life during the night and early morning.

Inhaled corticosteroids were introduced for the treatment of asthma around 15 years ago. Topically active steroids were used initially to replace oral steroids in patients with severe chronic asthma. The inhaled route is considered to be much safer than the oral route for steroid treatment^{1,2} and over the last few years physicians have recommended the earlier introduction of inhaled steroids to patients with less severe or moderate asthma.³⁻⁵ There is growing evidence that inhaled corticosteroids decrease airway hyperreactivity,⁶⁻⁸ and to a greater extent than beta₂ agonists.⁹ The safety margin with topical application is high owing to low systemic concentrations of the drug. The safety margin also increases when the elimination rate from the body is high, as with budesonide.¹⁰

Our study was undertaken to investigate the effects of low doses of inhaled corticosteroids in outpatients with mild symptomatic asthma treated with inhaled beta₂ agonists only.

Methods

PATIENTS

The inclusion criteria were a beta₂ agonist consumption of at least 35 puffs during the run in week and a mean variation of 10-30% in peak expiratory flow (PEF) over the last four days of the run in week with a mean PEF of at least 75% of predicted normal values.¹¹ The patients had to be compliant and to have filled in their diary cards correctly during the run in week. Patients were excluded if they were receiving inhaled or oral corticosteroids or using spacers for beta₂ agonist administration. We also excluded patients with important concomitant diseases likely to interfere with the accomplishment of the study and those who had had a respiratory infection or an acute asthma exacerbation during the month before the start of the study.

The patients gave their informed consent. Approval for the study, which was conducted according to the Declaration of Helsinki (1975), was obtained from the regional ethics committee.

STUDY DESIGN

The study had a multicentre, randomised, double blind, parallel group, placebo controlled design, consisting of six treatment weeks (placebo, or twice daily budesonide 100 or 200 µg). It started with one run in week if the patient's medication was an inhaled beta₂ agonist only. If the medication also included oral bronchodilators, these were replaced by an inhaled beta₂ agonist during a washout week before the run in week. To increase peripheral lung and decrease oropharyngeal deposition of budesonide, the patients were instructed to use a 750 ml spacer (Nebuhaler) connected to a metered dose inhaler for inhalation of the study drug. The beta₂ agonist on a regular or "as required" basis (or both) was administered by a metered dose inhaler without a spacer. Patients were also instructed about the sequence of peak flow measurement and drug administration (namely, PEF measurement followed by inhalation of beta₂ agonist (if needed) and then by inhalation of budesonide). The patients were treated by general practitioners at health care centres and chest physicians at lung clinic outpatient departments.

Health Care Centre,
Älmhult, Sweden
Sture Lorentzson

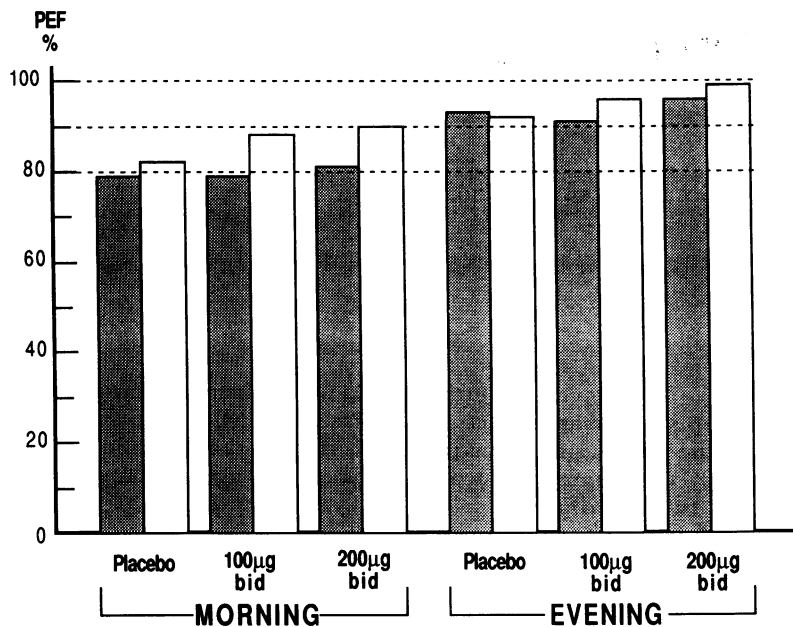
Department of Lung
Medicine, University
of Trondheim, Region
Hospital, Trondheim,
Norway
J Boe

Medical Department,
AB Draco, Lund,
Sweden
G Eriksson

Allergy Section,
Medical Department,
University of Lund,
Sweden
G Persson

Address for reprint requests:
Dr S Lorentzson,
Vårdcentralen, S-343 00
Älmhult, Sweden.

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Peak expiratory flow (PEF) values as percentage of predicted normal before (■) and after (□) six weeks' treatment with placebo or budesonide 100 or 200 µg twice daily (bid).

Evaluation procedures

For seven weeks (one run in week and six treatment weeks) the patients recorded PEF in the morning and early evening (best result of two attempts) using a mini Wright peak flow meter. Beta₂ agonist consumption was recorded as the number of puffs taken from the time of

the morning peak flow measurement until bedtime (day registration) and from bedtime until the following morning peak flow measurement (night registration). Subjects also recorded an asthma symptoms score according to a four grade scale (0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms). Adverse experiences were recorded daily. Diary cards were mailed to the doctor after two and four weeks, and brought to the clinic at the last visit after six weeks of treatment.

The patients made three visits to the clinic during the trial. At visit 1 patients were informed of the purpose of the study and instructed in the use of the peak flow meter and how to score asthma symptoms and report adverse experiences. At visit 2 one week later (two weeks later if oral bronchodilators had to be replaced by inhaled beta₂ agonist) the diary cards were checked carefully, and if the inclusion criteria were fulfilled the patient was randomly allocated to one of the three treatment groups. They were then equipped with a budesonide canister (of identical appearance for placebo and active drug), a spacer, and three diary cards (for three fortnights) and informed about inhalation technique. Patients were also carefully instructed on how their beta₂ agonist should be taken in case of need—that is, by slowly decreasing the number of puffs during phases of improvement and increasing them rapidly during deterioration. At visit 3 the patients were asked to assess the six weeks of treatment in relation to the run in week according to whether their asthma was much improved, improved, unchanged, worse, or much worse.

Table 1 Mean (SEM) baseline values in the three groups and all the subjects combined

	Placebo group	Budesonide groups (twice daily dose)		All subjects
		100 µg	200 µg	
Number of patients	33	32	38	103
Age (y)	33.8 (2.2)	32.0 (2.2)	30.6 (1.9)	32.0 (1.3)
Duration of asthma (y)	8.6 (1.1)	12.3 (2.0)	12.0 (1.6)	11.0 (0.9)
Peak flow (l/min)				
morning (l/min)	397 (16)	398 (16)	429 (16)	409 (9)
(% predicted)	79 (2)	79 (3)	81 (2)	80 (1)
evening (l/min)	466 (16)	462 (17)	507 (17)	479 (10)
(% predicted)	93 (2)	92 (3)	96 (2)	94 (1)
Beta ₂ agonist (puffs)				
Day	8.1 (0.8)	10.1 (1.0)	9.3 (1.0)	9.2 (0.6)
Night	1.4 (0.3)	3.9 (0.9)	2.8 (0.6)	2.7 (0.4)
Symptom score				
Day	1.0 (0.1)	1.1 (0.1)	1.2 (0.1)	1.1 (0.1)
Night	0.6 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)

Table 2 Change in mean (SEM) peak expiratory flow (PEF), beta₂ agonist use, and asthma symptom score over the six weeks of treatment

	Placebo group	Budesonide groups (twice daily dose)	
		100 µg	200 µg
PEF (l/min)			
Morning	15 (10)	36 (8)	47 (9)*
Evening	− 4 (10)	14 (7)	13 (6)
Beta ₂ agonist (puffs)			
Day	− 1.2 (0.6)	− 4.7 (1.1)	− 4.2 (0.8)
Night	0.6 (0.5)	− 2.3 (0.7)***	− 1.7 (0.4)***
Symptom score			
Day	0.0 (0.1)	− 0.3 (0.1)	− 0.3 (0.1)*
Night	0.0 (1.1)	− 0.4 (0.1)**	− 0.4 (0.1)**

Significance in the comparison with placebo: *p < 0.05; **p < 0.01; ***p < 0.001.

ANALYSIS

The main variables analysed were PEF and beta₂ agonist consumption. The effectiveness of treatment was assessed by both within group and between group analysis with appropriate parametric (*t* test) and non-parametric (van Elteren test, a stratified Wilcoxon test) statistics. The level of significance was set at 5%.

Results

One hundred and four patients with mild symptomatic asthma entered the study. The mean age was 32 (range 16–59) years and the mean duration of asthma 11 (range 1–38) years. One hundred and three patients (58 men and 45 women) completed the study, one patient dropping out after two weeks for unknown reasons. Baseline values are shown in table 1.

The PEF values, number of beta₂ agonist inhalations, and symptoms showed no significant changes during the placebo treatment. Morning PEF increased by 36 l/min (NS) and 47 l/min (p < 0.05) after six weeks' treatment with 200 and 400 µg budesonide daily by comparison with placebo. Evening PEF values did not change significantly between treatments (table 2).

Nocturnal beta₂ agonist consumption decreased significantly by comparison with placebo after both 200 and 400 µg budesonide,

from 3.9 to 1.6 puffs and from 2.8 to 1.1 puffs ($p < 0.001$). Beta₂ agonist consumption, during the day only, fell significantly after 400 µg budesonide by comparison with placebo (table 2).

The night time asthma symptoms score decreased from 0.8 to 0.4 after both doses of budesonide ($p < 0.01$) by comparison with placebo. Day time recordings fell significantly in relation to placebo only after 400 µg budesonide (table 2).

Assessment of asthma after six weeks of treatment showed that 66% of patients taking budesonide were improved (30% much improved and 36% improved). In the placebo group 30% improved. The placebo effect was significantly less than the effect of active treatment ($p < 0.01$). We found no significant differences between the active treatments.

There was no report of adverse experiences among the budesonide treated patients that could be connected with the drug or additives. In the placebo group two patients reported a sore throat.

Discussion

There is increasing evidence that epithelial damage, along with extravasation of plasma, bronchial oedema, and cell infiltration, may be present even in mild asthma.¹² Neither beta₂ agonists nor theophyllines have the same anti-inflammatory and antiasthmatic effects as corticosteroids.¹³ Inhaled budesonide has been shown to be effective in patients with severe asthma dependent on oral steroids and in those with moderate asthma, exercise induced asthma, and allergic asthma.^{4,14}

Some patients with mild asthma have episodic attacks only and may experience long symptom-free periods. Other patients with relatively mild disease have some daily symptoms and are often treated with inhaled beta₂ agonists. In our study we tried to include such a population of subjects with mild but symptomatic asthma and nearly normal lung function during the day but with increased symptoms at night.

We thought that such patients might improve with relatively small doses of budesonide. The mean peak flow at entry was 80% of predicted in the morning and 94% in the evening. Despite the relatively normal PEF values at entry into the study, values increased during treatment with budesonide. The need for a beta₂ agonist was significantly reduced during the night, and nocturnal asthma symptoms also decreased, suggesting that patients thereby experienced more nights with undisturbed sleep.

The objective results corresponded well with the patients' assessment of asthma severity after six weeks of treatment: 30% were much improved and a further 36% improved. Thus two thirds of the patients treated with budesonide experienced an improvement of their asthma after a relatively short period of treatment, but only one third of the patients given placebo. Thus when an inhaled corticosteroid is introduced at a relatively early stage to patients with mild symptomatic asthma night time symptoms and early morning PEF may be expected to improve and the need for beta₂ agonists to decline.

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