

Budesonide treatment of moderate and severe asthma in children: A dose-response study

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Objective: The purpose of the study was to evaluate the dose-response relationships of the inhaled corticosteroid budesonide in a double blind crossover study in 19 children with moderate and severe asthma.

Methods: A 2-week placebo treatment period (run-in) was followed by three 4-week treatment periods during which 100, 200, and 400 µg of budesonide were given per day in randomized order. Urinary cortisol excretion, lung functions, and protection against exercise-induced asthma were assessed at the end of run-in and each treatment period. Furthermore, morning and evening peak expiratory flow rates, day and night symptoms, and use of rescue β_2 -agonists were recorded throughout the study.

Results: One hundred micrograms of budesonide per day markedly improved symptoms, morning and evening peak expiratory flow rates, and use of rescue β_2 -agonists ($p < 0.01$). No further improvement was seen in these parameters with increasing doses of budesonide. In contrast, a significant dose-response effect was found on lung functions measured at the hospital and fall in lung functions after exercise ($p < 0.001$); 200 µg was significantly better than 100 µg, and 400 µg was significantly better than 200 µg. About 53% of the maximum effect against exercise-induced asthma was achieved by the lowest budesonide dose ($p < 0.001$), and about 83% by the highest dose. No significant differences were seen in urinary cortisol excretion between run-in and the various budesonide doses.

Conclusions: Low doses of budesonide, which are not associated with any systemic side effects, have a marked antiasthma effect in children. Protection against exercise-induced asthma requires higher doses than achievement of symptom control. (*J ALLERGY CLIN IMMUNOL* 1995;95:29-33.)

Key words: Asthma, children, corticosteroids, dose-response, exercise-induced asthma

Because it has been recognized that inflammation is an important feature of the airways of asthmatic patients, inhaled corticosteroids are being recommended for early use in treatment when a patient requires regular use of an inhaled β_2 -agonist to control asthma symptoms.^{1,2} However, at present little is known about the optimal dose of inhaled corticosteroid in children because no dose-response studies have been performed in this age group. Such studies are important for appropriate

Abbreviations used

b.i.d.:	Twice daily
FEF ₂₅₋₇₅ :	Forced expiratory flow rate between 25% and 75% of FVC
FEV ₁ :	Forced expiratory volume in 1 second
FVC:	Forced vital capacity
PEFR:	Peak expiratory flow rate

risk-benefit evaluations. So far the vast majority of studies have only assessed the risk of systemic side effects of the treatment without accurate assessment of the clinical response to various doses of inhaled corticosteroid. Therefore the aim of this study was to assess the dose-response relationships of the inhaled corticosteroid budesonide in children with moderate asthma.

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METHODS

Children between the ages of 6 and 15 years who had symptoms (cough not counting in this respect) at least 3 days per week, and a bronchial reversibility of 20% or greater after inhalation of 2 puffs of terbutaline or a fall of more than 20% in forced expiratory volume in 1 second (FEV₁) after a standardized exercise test were included in the study. All were new referrals, who were using an inhaled β_2 -agonist as needed. No other regular treatment was given.

Children with bronchopulmonary diseases other than asthma and patients who had received oral prednisolone within 1 month before the study were excluded. The study was approved by the ethics committee, and informed consent was obtained from all children and their parents.

The trial was a randomized, double-blind, crossover study consisting of a 2-week run-in period and three consecutive 4-week treatment periods. Throughout the study inhaled terbutaline was used on demand; otherwise, no other asthma treatment was allowed. During the three active treatment periods, budesonide in doses of 50 μ g twice daily (b.i.d.), 100 μ g b.i.d., and 200 μ g b.i.d. were given in randomized order from a metered-dose inhaler with a large volume spacer (Nebuhaler; ASTRA Pharmaceuticals, Lund, Sweden) attached. The drug was packed in identical canisters, and in all three periods the dose was 1 puff in the morning and 1 puff in the evening.

The children visited the clinic at the start and end of run-in and at the end of each treatment period. Pulmonary functions (FEV₁, forced vital capacity [FVC], forced expiratory flow rate between 25% and 75% of FVC [FEF₂₅₋₇₅], and peak expiratory flow rate [PEFR]) were determined, and a standardized exercise test was performed at each visit. Inhaled bronchodilators were not allowed for 6 hours before lung function measurements or exercise tests. Furthermore, urinary cortisol excretion was measured at the end of run-in and at the end of each active treatment period. Daytime urine and nighttime urine were collected in separate preweighed bottles. To increase the accuracy, urine was always collected on 2 consecutive days.

The exercise test was a 6-minute treadmill test. The workload was adjusted to produce a pulse rate of 170 beats/min or more during the last 3 minutes of exercise. Each child wore a nose clip during the test, and the temperature and air humidity were recorded. Lung functions were measured before the test and 1, 3, 5, 8, 10, 15, and 20 minutes after the test or until a maximum fall had occurred. Two reproducible lung functions were obtained, and the one with the highest FEV₁ was used for calculations. The maximum absolute fall and percent fall in the various pulmonary function parameters were analyzed.

Compliance with the dosing regimens was checked by weighing the metered-dose inhaler canisters before and after the study.

Throughout the study diary recordings of daytime symptoms (0 to 6), nighttime symptoms (0 to 5), morning

and evening PEFR (best of three measurements), and the requirement of rescue terbutaline were made. The last 14 days of each period were used for evaluation.

Statistics

Lung function data at the clinic and the data from the exercise tests were compared between randomized treatments by assuming a multiplicative analysis of variance model with the factors patient, period, and treatment and then estimating the treatment effect. When run-in was compared with the other treatments a multiplicative analysis of variance model with factors patients and treatment was used, followed by pairwise comparisons between treatments. This analysis assumes that there is no period effect.

For diary data the observations from day 14 to day 21 were analyzed in the same way as lung function data. For PEFR the model was multiplicative, but for the remaining variables the model was additive.

RESULTS

Seventeen boys and two girls fulfilled all inclusion criteria and were randomized to active treatment after the run-in period. All children demonstrated 20% or greater bronchial reversibility (range, 26.5% to 82.4%), as well as a fall of 20% or greater in FEV₁ (range, 22.5% to 76.5%) after exercise. One boy was withdrawn from the study during the last period when he was treated with 50 μ g b.i.d. because of a fall in morning PEFR of more than 30%, unacceptable increase in symptoms, and daily use of more than 8 puffs of rescue terbutaline.

The age of the children varied from 6 to 14 years (mean, 11 years), and the mean duration of asthma was 7.5 years (range, 4 to 12 years). Height varied from 126 to 178 cm (mean, 150 cm), and weight from 25.3 to 60.0 kg (mean, 37.5 kg). Compliance was high (>80%) in all children and without any differences among the three dose regimens.

No period effects were observed and no carry-over effects were found for any of the active treatments.

Recordings at the clinic

The mean pulmonary functions measured during the five visits at the clinic are shown in Table I. No significant changes were seen during run-in. Compared with run-in, a statistically significant dose-dependent increase was seen in all values ($p < 0.01$); this increase was already significant at doses of 50 μ g b.i.d. and 200 μ g b.i.d. and was significantly better than 50 μ g b.i.d. Furthermore, for FVC and FEF₂₅₋₇₅ there was a trend that 200

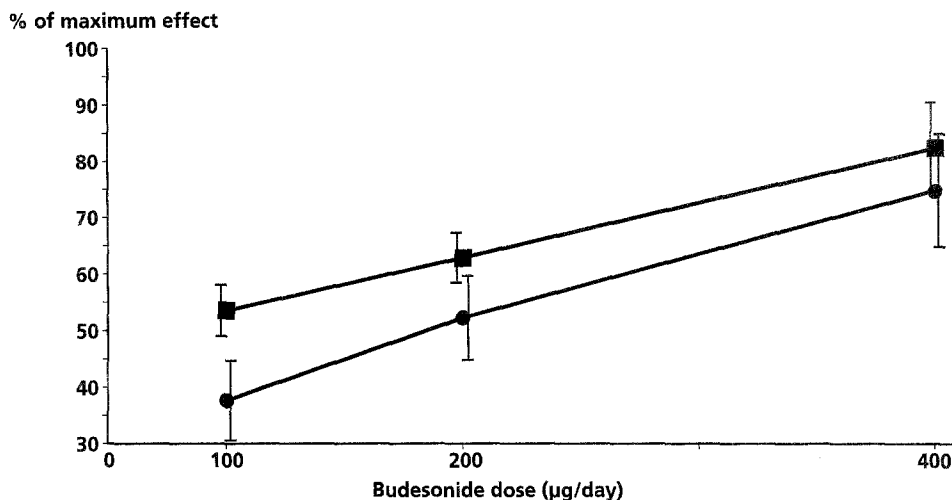


FIG. 1. Percent of maximum achievable protection (mean and 95% confidence limits) against fall in FEV₁ (■) and FEF₂₅₋₇₅ (●) after exercise in 19 children treated with 100, 200, and 400 µg of budesonide per day in randomized sequence. Each treatment period was 4 weeks.

TABLE I. Mean lung function parameters and percent fall in lung functions after a standardised exercise test in 19 children treated with placebo (run-in) and three different doses of budesonide

	Run-in		Treatment period			p Value (100 vs 400 µg)
	Start	End	100 µg/day	200 µg/day	400 µg/day	
FVC (L)	2.25	2.26	2.50*	2.59	2.72	0.002
FEV ₁ (L)	1.60	1.64	1.93†	2.00	2.14	0.006
FEF ₂₅₋₇₅ (L/min)	1.14	1.19	1.55†	1.68	1.87	0.01
PEFR (L/min)	198	206	267*	289	314	0.11
PEFR (% pred)	55.1	57.1	72.6*	78.6	87.0	0.09
Fall in FEV ₁ (%)		55.4	25.7‡	20.1*	9.9‡	< 0.001
Fall in FEF ₂₅₋₇₅ (%)		36.3	39.7‡	29.9‡	16.1‡	< 0.001

* $p < 0.01$ compared with the previous column.

† $p < 0.001$ compared with the previous column.

‡ $p < 0.0001$ compared with the previous column.

µg b.i.d. was significantly better than 100 µg b.i.d. ($p = 0.05$ and 0.08 , respectively).

The results of the exercise test are shown in Table I and Fig. 1. As for lung function, a statistically significant dose-related reduction was seen in percent fall in FEV₁ and FEF₂₅₋₇₅ ($p < 0.001$), with a dose of 200 µg b.i.d. producing 83% and 75% of the maximum achievable protection against fall in FEV₁ and FEF₂₅₋₇₅, respectively. The exercise test was more sensitive than the lung function measurements in detecting differences between the various treatments: 50 µg b.i.d. offered significant protection in comparison with run-in, 100 µg b.i.d. was significantly better than the 50 µg b.i.d., and 200 µg b.i.d. offered more protection than 100 µg b.i.d.

The absolute change in lung function values was assessed in the same way as the percent change, and the conclusions were the same.

Diary recordings

The mean results of the diary recordings are shown in Table II. Mean morning PEFR varied from 72% to 40% of the predicted normal value (mean = 52%). Furthermore, all subjects required frequent use of rescue terbutaline (varied from 5 to 18 puffs/day; mean = 9.2 puffs/day), indicating that all children had moderate or severe asthma during run-in. All doses produced a statistically significant improvement in all variables ($p < 0.001$). However, no significant differences were

TABLE II. Mean diary recordings in 19 children treated with placebo (run-in) and three different doses of budesonide

	Mean diary recordings				
	Morning PEFR (L/min)	Evening PEFR (L/min)	Day symptoms (0-6)	Night symptoms (0-4)	Terbutaline use (puffs/day)
Run-in	186.8*	221.3*	2.75*	1.82*	9.23*
100 µg/day	283.7	303.8	1.20	0.62	2.3
200 µg/day	279.8	279.8	1.09	0.64	2.26
400 µg/day	280.2	292.5	1.24	0.74	2.83

*Significantly different from the three active treatments ($p < 0.001$).

found among the three dose levels. The results were also analyzed by using the last week instead of the last 2 weeks in each period, but the conclusions were the same.

Urinary cortisol excretion

As for the clinical parameters, no period or carryover effects were found. There were no statistically significant differences among the four periods when daytime and nighttime cortisol excretion were analyzed separately or when they were pooled. The mean ($\pm$ SD) 24-hour urinary cortisol excretion values during run-in 50, 100, and 200 µg b.i.d. were 66.8 ± 23 , 76.3 ± 21 , 70.1 ± 23 , and 68.1 ± 20 nmol, respectively, when corrected for creatinine excretion, the values were 13.1 ± 3.9 , 14.7 ± 4.9 , 13.1 ± 4.5 , and 13.0 ± 3.4 nmol cortisol/mmol creatinine, respectively.

DISCUSSION

To our knowledge this is the first clinical dose-response study of budesonide in children with moderate and severe asthma. The results showed that in such children even low doses, around 100 µg/day, produce quite a marked effect on symptoms and lung functions, as well as on bronchial hyperreactivity. The diary recordings showed that all children had daily symptoms and reduced lung function during run-in and at study entry. There was no improvement in the condition during run-in, indicating that the clinical condition was stable before the children were allocated to active treatment. Furthermore, the marked fall in FEV₁ after exercise emphasized that the asthma of the patients was sufficiently severe to make them suitable for a dose-response study.

It was unexpected that the lowest dose of budesonide had such a marked effect that the top of the dose-response curve was already reached at that dose level for the majority of the parameters

studied. No further improvement was seen in diary recordings with increasing dose. This is in good agreement with the findings in dose-response studies in large numbers of adults.^{3,4} Boe et al.³ did not find any statistically significant differences between the effect of daily doses of 400 to 800 µg of budesonide or between 400 and 1000 µg of beclomethasone on PEFR and diary recordings. The lowest dose of both drugs produced a marked and statistically significant effect. The same was the case in the study of Dahl et al.,⁴ which assessed the effect of 100 to 800 µg of fluticasone propionate per day in 672 patients. Though a statistically significant dose-response relationship was found, the mean difference in morning PEFR between the lowest and the highest dose was only around 14 L/min, and no statistically significant differences between individual dose steps were found.⁴ These findings are important to remember when comparisons between various inhaled corticosteroids are made. It will be difficult to show any differences between two drugs, two doses of the same drug, or a high dose of one drug and a low dose of another if only PEFR measurements and diary recordings are assessed. In such studies false conclusions about equieffective doses may be made on the basis of the finding of "no difference" between treatments.

FVC, FEV₁, and FEF₂₅₋₇₅ seemed to be somewhat more sensitive parameters for detecting differences between the various doses. However, the effect on airway hyperreactivity, as assessed by protection against exercise-induced asthma, was by far the most sensitive parameter for detecting differences between the various budesonide doses. A log linear dose-response curve was found. The slope was quite steep, so that statistically significant differences were found between individual dose steps. Therefore a standardized exercise test and measurements of FVC, FEV₁, and FEF₂₅₋₇₅

should be included in comparative studies of inhaled corticosteroids or inhalers delivering inhaled corticosteroids. This will make the study more sensitive in detecting differences and will reduce the risk of erroneous conclusions about equieffective doses.

This study did not include a sufficient number of patients to allow a subgroup analysis to determine whether the dose-response characteristics differed, depending on asthma severity. However, for the exercise tests the slopes of the individual dose-response curves did not vary significantly with the initial degree of exercise-induced asthma ($p = 0.53$).

The protective effect of inhaled corticosteroids on exercise-induced asthma is time-dependent,⁵ and it is possible that the protection would have been even more pronounced if the treatment period had been extended and that even better protection would have been achieved by the lower doses. This would be expected because the low doses produced a good clinical improvement and there seems to be a correlation between change in clinical condition and degree of exercise-induced asthma.⁶ However, the lack of a period effect in our study suggested that it would require treatment longer than 2 additional months to increase the protection significantly. Under the conditions of the study 85% of the maximum achievable effect was obtained with a daily budesonide dose of 400 μ g or less to achieve optimal asthma control. This is an important finding because these doses have been found to be without any systemic side effects in earlier studies,^{7,8} as well as in this study, in which no significant effects were found on urinary cortisol excretion.

Perhaps the study would have been more sensitive in detecting differences between the various doses if longer treatment periods had been used or if washout periods between the active treatments had been included. We did not extend the treatment period because that would have increased the

risk of influence of seasonal variations in symptoms, which are common in Denmark. A washout period was not included because we did not appreciate the importance of this at the time the study was designed. However, we did not find any carryover or period effects, and the results are in agreement with the results from dose-response studies of parallel group designs in adults.⁴ Thus we do not believe that the lack of a washout period affected our conclusions to any clinically significant extent. Therefore we find it safe to conclude that low doses of inhaled budesonide from a Nebuhaler produce a marked clinical effect and that about 85% of the maximum achievable effect is obtained by 4 weeks of treatment with 400 μ g of budesonide per day in children with severe asthma. Furthermore, these doses do not adversely affect urinary cortisol excretion.

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