

Rapid induction of clinical response with a short-term high-dose starting schedule of budesonide nebulizing suspension in young children with recurrent wheezing episodes

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Background: There are no data currently available on the correct schedule for the initiation of treatment with nebulized suspension of budesonide in children with recurrent wheezing episodes. We compared the efficacy and safety of starting with a high dose followed by a stepwise decrease to a continuous low dose.

Methods: In a double-blind design, 42 children aged 6 months to 3 years were randomly allocated to receive either a high starting dose of 1 mg budesonide twice daily followed by a stepwise decrease of 25% every second day for 1 week (group A) or a low dose of 0.25 mg twice daily for 1 week (group B). Efficacy was assessed with daily symptom scores and the systemic effect of the corticosteroids with the adrenocorticotrophic hormone test.

Results: The two groups were comparable for all parameters evaluated. During the first week of treatment, there was a significant decrease in asthmatic symptomatology only in group A: a 59% decrease for wheezing ($p = 0.0001$), 39% for diurnal cough ($p = 0.036$), and 39% for nocturnal cough ($p = 0.04$). Mean time to clinical response was 3.0 days in group A and 5.7 days in group B ($p = 0.02$). This early improvement was sustained for the rest of the follow-up period. The high dose starting schedule was not associated with any change in serum cortisol level.

Conclusions: The administration of nebulized suspension of budesonide at a high starting dose schedule followed by a rapid (1 week) stepwise decrease yields a significant early improvement in asthma symptoms and causes no change in serum cortisol levels. (*J Allergy Clin Immunol* 1998;101:464-9.)

Key words: *Inhaled corticosteroids, budesonide nebulizing suspension, dose schedule, treatment, children, wheezing, asthma*

It is now generally accepted that antiasthmatic treatment should be directed at reversing the underlying

Abbreviation used

ACTH: Adrenocorticotrophic hormone

inflammation, not simply relieving bronchospasm,¹ and the early introduction of aerosol corticosteroids such as budesonide, which have a high topical antiinflammatory potency and a low systemic bioavailability, is strongly recommended.^{2,3} The use of aerosols in children younger than 3 to 4 years has been associated with technical difficulties.^{4,5} Nebulization is a very suitable inhalation technique in young patients who are unable to use a metered dose inhaler with a mask,⁶ and recent controlled studies have shown that nebulized suspensions of 0.25 and 1.0 mg budesonide are effective in the management of moderate to severe asthma in this age group.^{7,8} In one double-blind study, only a trend in favor of 0.25 mg budesonide twice daily was observed as compared with placebo.⁹ Starting doses in children have ranged between 0.5 and 2.0 mg per day.⁷⁻¹² Almost no information is available as yet on the preferred dose schedule for the initiation of treatment when continuous prophylactic therapy is needed.

The aim of this double-blind study was to compare the efficacy and safety of starting with a high dose of nebulized budesonide, followed by a stepwise decrease to a continuous low dose.

METHODS

Patients

We studied children who attended our outpatient asthma clinics because of recurrent wheezing episodes. Children 6 months to 3 years of age, with at least three wheezing episodes and asthmatic symptomatology on more than 40% of the days during the previous 3 months and a total symptom score (see study design) of more than 21 for the 3-week pretrial run-in period, were included in this study. Children were excluded if they had used inhaled corticosteroids, sodium cromoglycate, or ketotifen during the 4 weeks preceding the study; if they had used oral corticosteroids for more than 5 days; if they had acute viral infection, pneumonia, or chronic pulmonary disease such as bronchopulmonary dysplasia, cystic fibrosis, or active or quiescent tuberculosis; or if they had a history of prematurity. The study was approved by the hospital's ethics committee for clinical investigation, and written informed consent was obtained from the parents of each child.

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Study design

The study followed a randomized double-blind design and was conducted in three phases. In the 3-week run-in period, patients continued to use their previous antiasthma medications, and the severity of disease was assessed by diary cards. In the first treatment week, patients were divided into two groups, with random numbers in blocks of eight. Group A started with a high dose of budesonide suspension of 2.0 mg/day (1.0 mg twice daily) with a 25% decrease in dose every 2 days until the sixth day, when a dose of 0.25 mg twice daily (the maintenance dose) was reached; group B received the maintenance dose of 0.25 mg twice daily from the beginning of the study. In the 9-week maintenance therapy period, patients in both groups received the maintenance dose of 0.25 mg twice daily.

Throughout the study, including the run-in period, in cases of inadequate control of the asthmatic symptomatology or of acute exacerbation, the following medications were permitted: (1) nebulized terbutaline solution (Bricanyl) in respules containing 0.25 mg in 2 ml volume terbutaline as needed and (2) increased dose of budesonide suspension (0.5 mg budesonide four times daily), with 25% decrease every day for 4 days.

At the beginning of treatment, all patients were given eight outwardly identical drug packets containing four respules each, assigned for use on each one of the days of the first treatment week (two respules twice daily). Patients in group A received respules of a combined budesonide suspension and saline solution containing 2, 1.5, 1, and 0.5 mg of budesonide to be taken on days 1 and 2, 3 and 4, 5 and 6, and 7 and 8, respectively; patients in group B received respules of 0.25 mg. During the 9-week follow-up period, all patients received respules of 0.25 mg budesonide twice daily. The budesonide suspension was administered by a home nebulization apparatus, the Ventstream Nebulizer (Medicaid) with sealing mask, which delivers 2 ml of budesonide suspension in 4 minutes. The same nebulizer was also used to administer bicalin when needed.

Starting from the run-in period, the parents were asked to keep a daily record of the children's symptoms (wheezing and diurnal and nocturnal cough), the use of bronchodilator drugs and prednisone, and possible side effects. The clinical symptoms were evaluated by the parents on a scale of 0 to 3 (0 = none/no, 1 = mild/occasional, 2 = moderate/frequent, and 3 = severe/constant). A similar scale was used on physical examination for findings of dyspnea, wheezing, rales, or nasal discharge. Patients were assessed on admission, at the end of the run-in period, at the end of the first treatment week, at 3-week intervals during the 9-week maintenance period, and at every episode of acute exacerbation.

To evaluate the rate of clinical response to therapy, time to clinical response was defined for each child as the number of days until he or she had a total daily symptom score of 7 for 7 consecutive days. Compliance was assessed by calculating the number of respules used (empty respules returned) compared with the number of respules prescribed. If compliance was below 80%, the patient was excluded from the analysis. To evaluate safety, the following laboratory examinations were performed before and immediately after the first treatment week: adrenocorticotrophic hormone (ACTH) test (fasting serum cortisol concentration at 8 am and 1 hour after intravenous administration of 0.25 mg Cortosyne) and other laboratory tests (fasting blood glucose and blood levels of sodium, kalium, chloride, calcium, phosphate, alkaline phosphatase, transaminases, total protein, albumin, cholesterol, and triglycerides).

TABLE I. Demographic and admission data

	Group A	Group B	p
No. of children	21	21	
Sex			
M	14	14	
F	7	7	
Age (mean $\pm$ SD)	21.52 $\pm$ 9.39	17.05 $\pm$ 8.94	0.12*
Weight (kg)	11.85 $\pm$ 2.35	11.05 $\pm$ 2.25	0.27*
(mean $\pm$ SD)			
Height (cm)	84.38 $\pm$ 9.98	79.24 $\pm$ 9.28	0.09*
(mean $\pm$ SD)			
Asthma in family (No. of children)	16	15	0.7†
Percent of time during the 3 months before the study with			
Asthma symptoms	65% $\pm$ 18%	70% $\pm$ 21%	0.3‡
Use of β_2 -agonists	54% $\pm$ 21%	61% $\pm$ 21%	0.4‡
No. of exacerbations	6.86 $\pm$ 8.16	5.52 $\pm$ 4.59	0.8‡
No. of emergency department visits	1.60 $\pm$ 1.31	1.81 $\pm$ 1.17	0.5‡
No. of hospitalizations	0.43 $\pm$ 0.68	0.43 $\pm$ 0.68	0.6‡
Physical examination (mean $\pm$ SD score)			
Dyspnea	1.81 $\pm$ 0.68	2.05 $\pm$ 0.67	0.3‡
Wheezing	2.38 $\pm$ 0.92	2.80 $\pm$ 0.70	0.06‡
Rales	2.48 $\pm$ 0.75	2.48 $\pm$ 0.87	0.8‡
Nasal discharge	2.33 $\pm$ 0.80	2.10 $\pm$ 0.83	0.3‡

During the 3 months before the beginning of study, the study groups were similar in all parameters evaluated.

*Student's *t* test.

† χ^2 test.

‡Mann-Whitney test.

Statistical analyses

Initial comparison between treatment groups. Treatment groups were compared for demographic and clinical parameters at baseline and after the run-in period. Frequency counts (e.g., incidence of familial allergy history) were analyzed with the X^2 goodness of fit or Fisher's exact test. Differences between mean values for variables that were normally or near-normally distributed (e.g., age) were analyzed with the independent Student's *t* test. Differences between mean values for variables that were highly abnormally distributed (e.g., number of asthma exacerbations) were analyzed with the Mann-Whitney U test.

Comparison of findings between run-in period and first treatment week. This analysis was based on changes in symptoms and number of β_2 -inhalations (Student's *t* test) and changes in signs (Mann-Whitney U test).

Comparison of patterns of change during first treatment week. Data on symptoms and β_2 -inhalations were obtained daily during the first treatment week. Comparisons of changes over time between the two groups were conducted by analysis of variance with repeated measures.

Comparison of findings between onset of treatment and end of follow-up. Weekly means of the two groups for symptoms and use of β_2 -inhalations were compared with analysis of variance. All tests were two-tailed, and *p* values equal to or less than 0.05 were considered significant.

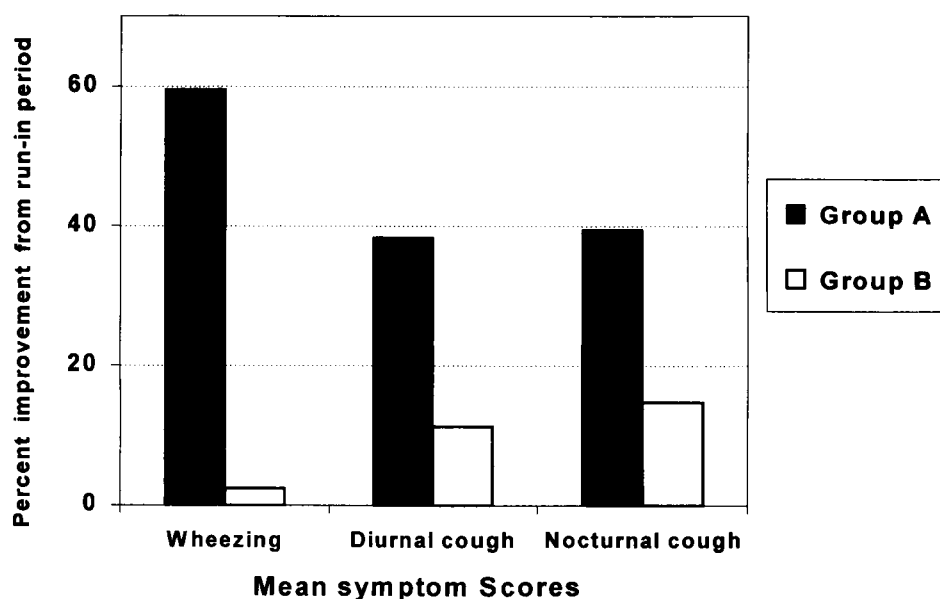


FIG. 1. Comparison of percent improvement in wheezing and diurnal and nocturnal cough from run-in period to first treatment week between two study groups.

RESULTS

The study cohort consisted of 42 children, 21 children (14 boys and 7 girls) in each group. Mean ages were 21.5 ± 9 months in group A and 17.1 ± 9 months group B. All children recruited for the study were included in the final analysis. One child contracted pneumonia and discontinued the study after the first 8 weeks, but he had completed all study protocol requirements until that time.

Initial comparison between treatment groups

During the 3 months before onset of the run-in period, the two groups were similar for all of the parameters evaluated (Table I), including the use of antiasthma medication (sodium cromoglycate, ketotifen, and oral corticosteroids). All children showed significant asthma symptoms (wheezing and diurnal and nocturnal cough) 65% of the time in group A and 70% of the time in group B. The use of β_2 -agonists was also similar: 54% and 61% of the time, respectively (Table I).

During the 3-week run-in period, the two groups were also comparable for all parameters evaluated. Asthma symptoms occurred 76% of the time in both groups, and β_2 -agonists were used 61% of the time in group A and 64% of the time in group B. Two children from group A and five from group B also used oral corticosteroids ($p = 0.2$) but not in the week just before initiation of treatment. Scores for asthma symptoms (wheezing and diurnal and nocturnal cough) and signs of physical examination (dyspnea, wheezing, rales, and nasal discharge) were similar for both groups. Serum cortisol concentrations before initiation of budesonide therapy were comparable in the two groups both for fasting levels at 8 AM

and at 1 hour after ACTH stimulation, as were all other laboratory test results.

Comparison of findings between run-in period and first treatment week

Children in group A demonstrated a significant improvement in mean asthma scores compared with the run-in period. Wheezing was improved by 59.5% ($p = 0.0001$), diurnal cough by 38.3% ($p = 0.036$), nocturnal cough by 39.4% ($p = 0.04$), and total symptom score by 45.5% ($p = 0.004$); number of inhalations of β_2 -agonists decreased by 66.9% ($p = 0.002$). In group B, corresponding figures were only 2.4%, 11.3%, 14.7%, 2.9%, and 43.7%, respectively. Fig. 1 shows the between-group difference in the rate of improvement for these major asthma symptoms. The mean total weekly scores for all symptoms were lower in group A during the first treatment week than in group B. However, only the difference for wheezing was significant ($p = 0.03$) (Fig. 2).

Comparison of the patterns of change during first treatment week

The mean symptom scores of each day of the first treatment week were compared with the mean symptom score of the first treatment day. A constant early decrease in asthma symptoms and in β_2 -agonist use was noted in group A (high starting dose) but not in group B. In group A mean wheezing score was significantly lower on days 2 through 7 as compared with day 1 ($p < 0.02$) (Fig. 3). A trend toward significance was also observed in group A in the diurnal cough score ($p < 0.09$) and in β_2 -agonist use ($p < 0.09$). The gradual decrease in the mean symptom

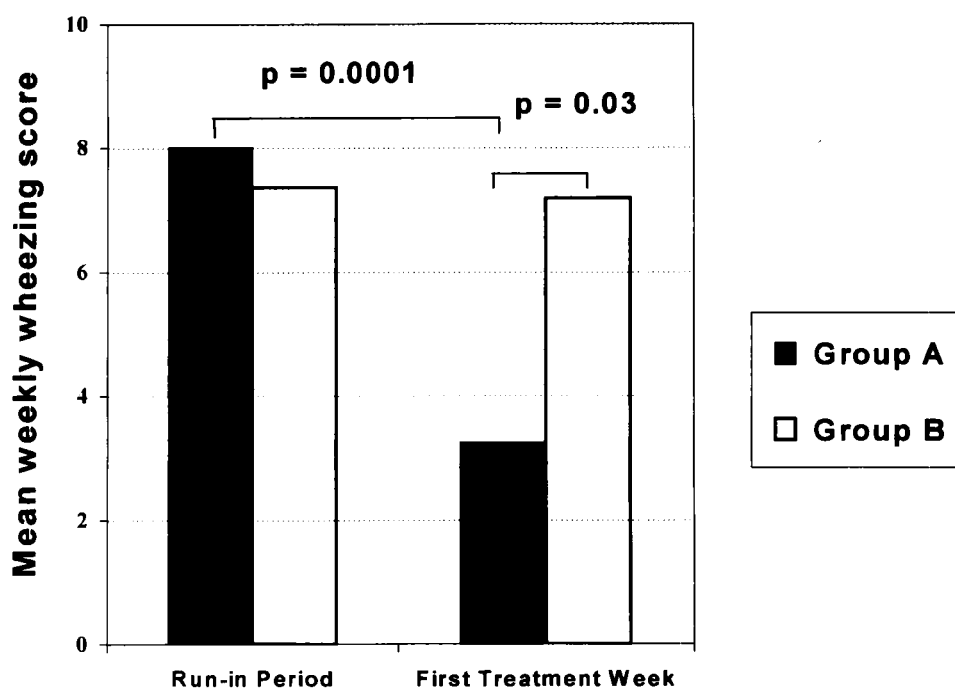


FIG. 2. Comparison of mean total wheezing score from run-in period to first week of treatment between two study groups.

score started from the second day of treatment in group A and from the fifth day in group B. The mean time to clinical response was 3.0 days in group A and 5.7 days in group B ($p = 0.02$). Physical signs (dyspnea, wheezing, rales, and nasal discharge) improved significantly in both groups in the first treatment week compared with the run-in period and remained mild throughout treatment. There was a similar negligible number of drug side effects in both groups. At the end of the first week of treatment, serum cortisol concentrations, both for fasting levels at 8 am and at 1 hour after ACTH stimulation, were similar to baseline values in both groups. All other laboratory examinations, including complete blood count and liver and kidney function tests, remained within normal limits in both groups.

Comparison of findings between onset of treatment and end of follow-up

After the first treatment week, a further gradual reduction in asthma symptoms was noted in both study groups. However, the mean symptom score, which was lower in group A at the end of the first treatment week, continued to be so for the remainder of the maintenance period, especially for wheezing (Fig. 4). The use of β_2 -agonists, which decreased at the end of the first study week in both groups, was maintained at a minimum throughout the remainder of the treatment period.

Children with asthma in the family

Sixteen children in group A and 15 in group B had a history of asthma in the family. Separate analyses of these subgroups yielded the same pattern of results as

for the whole groups. However, for most parameters, group A children with a family history of asthma demonstrated higher statistical differences than their counterparts in group B. Analysis of change over time during the first treatment week in these subgroups yielded significant improvements in wheezing ($p < 0.02$), diurnal cough ($p < 0.03$), and total symptom score ($p < 0.05$).

DISCUSSION

Many criteria should be taken into consideration when choosing a schedule for the initiation of nebulized budesonide suspension in young children who need continuous antiasthma therapy. What should the starting dose be? How many doses are needed per day? Should we apply a step-up or step-down schedule or use the same dose every day? If we start with a high dose, what should the rate of dose change be? What should the duration of the initial treatment period be before the maintenance dose is reached? What should the maintenance dose be? In this study we compared the efficacy and safety of two starting dose schedules with budesonide nebulization suspension: (1) a high starting dose of 1 mg twice daily with a rapid stepwise reduction of 25% every second day, reaching a dose of 0.25 mg twice daily after 6 days, and (2) a continuous dose of 0.25 mg twice daily for 1 week. The high dose schedule was chosen on the basis of our clinical experience with inhaled budesonide.^{13, 14} The high starting dose schedule was found to induce a significantly earlier clinical effect (from the second day of treatment) than the lower dose schedule (only in the fifth to sixth days of treatment),

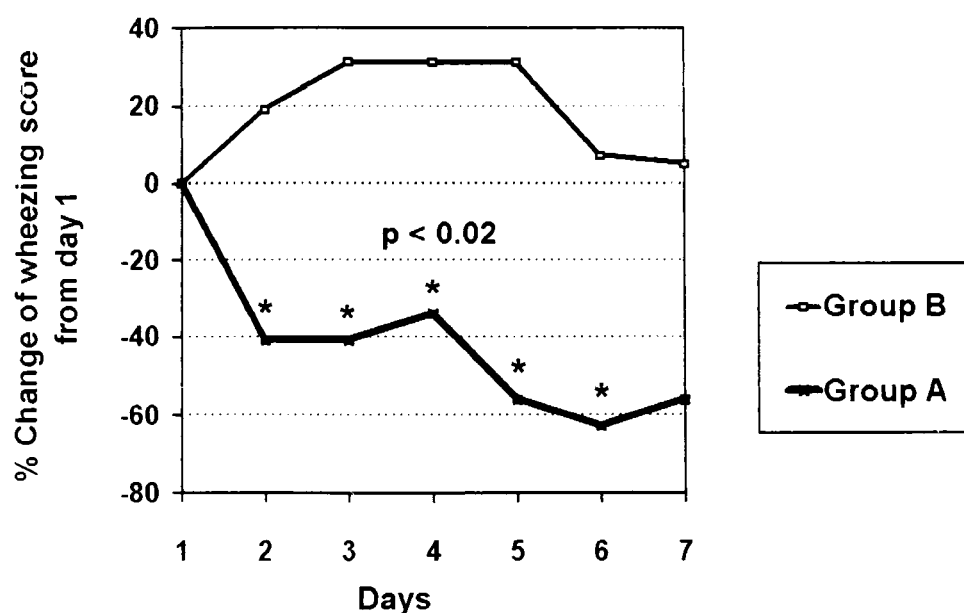


FIG. 3. Comparison of patterns of change in wheezing scores over first week of treatment between the study groups.

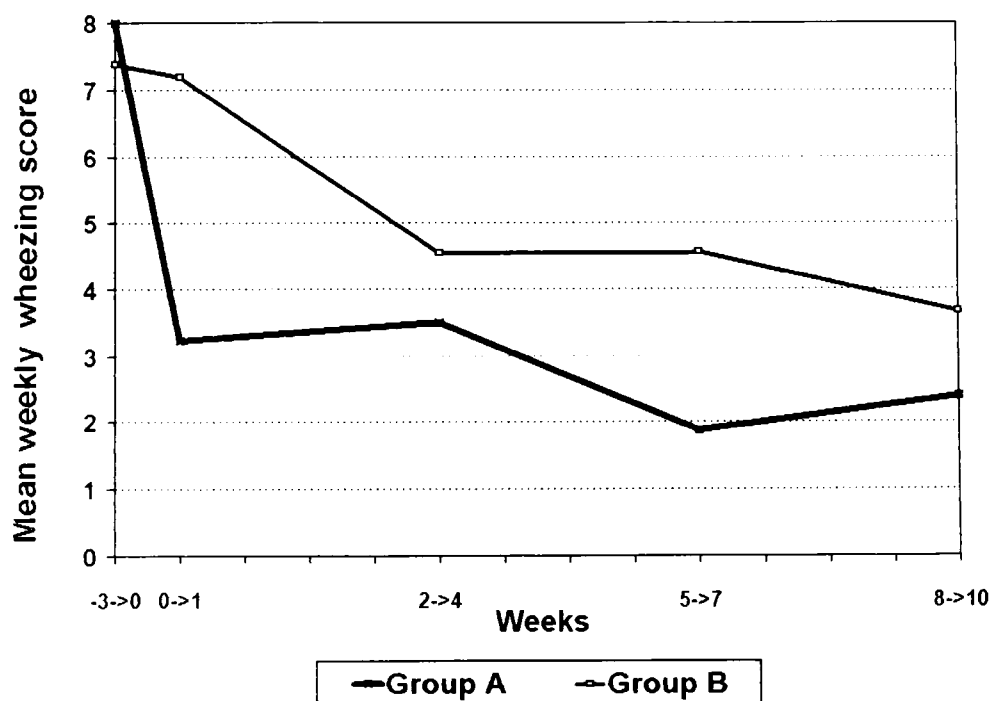


FIG. 4. Comparison of changes in mean weekly wheezing scores from beginning of treatment to the of follow-up between two study groups.

and the rapid improvement was sustained throughout the study period.

De Blic et al.⁷ claimed that the effect of nebulized budesonide solution can be observed only after 1 month of treatment, and Wennergren et al.⁸ found that 24 to 30

days passed before the complete disappearance of asthma symptoms. Yet a careful inspection of the data reveals that, like our cohort, their study children showed a remarkable improvement during the first days of active treatment.

Wheezing was the clinical symptom that showed the most significant improvement in the high-dose group compared with the maintenance group. De Blic et al.⁷ also found significant improvement in wheezing but not in cough, and Van Bever et al.⁹ noted a trend toward improvement only for wheezing. Cough was also affected by a high initial dose of budesonide suspension, but its improvement was less significant than that of wheezing. A possible explanation for this observation is the fact that cough in children may be due to other reasons such as upper respiratory infection, large tonsils, and adenoids, none of which respond well to antiasthma medication.

To evaluate the net influence of the budesonide treatment on the clinical outcome, we asked all children and their parents to avoid regular β_2 -agonist use during the entire treatment period unless absolutely necessary. We found that the overall use of β_2 -agonists in the first week of treatment was minimal and significantly lower than that found in the run-in period ($p = 0.0004$ for group A and $p = 0.001$ for group B). On the basis of this study design, we can conclude that it was the budesonide suspension that was mainly responsible for the amelioration of asthma in the initial treatment period and not the β_2 -agonist.

Earlier studies have shown that 1 mg of nebulized solution of budesonide given twice daily for a period of 18 months is associated with a much greater depression of cortisol than 0.25 mg twice daily.^{6,8} In our study a similar high dose given for only 1 week was found to be safe, as shown by the normal serum cortisol concentrations, both fasting at 8 AM and 1 hour after intravenous injection of ACTH analogue.

In conclusion, our study demonstrates that in children with recurrent wheezing episodes, therapy that consists of a relatively high initial dose of budesonide nebulization suspension (1 mg twice daily) followed by a rapid stepwise decrease in dose over 1 week is associated with an early clinical effect starting from the second day of

treatment. This clinical effect is maintained throughout the maintenance period. The proposed relatively high starting dose is safe, as reflected by the normal serum cortisol measurements.

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