# Effectiveness and safety of inhaled corticosteroids in controlling acute asthma attacks in children who were treated in the emergency department: A controlled comparative study with oral prednisolone

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**Background: Inhaled corticosteroids have a greater antiinflammatory potency and fewer systemic effects than intravenous, intramuscular, or oral corticosteroids. However, their role in acute asthma has not been established. We prospectively investigated the efficacy and safety of inhaled corticosteroids in controlling moderately severe acute asthma attacks in children who were treated in the emergency department.**

**Methods: Children who were treated in the emergency department with moderately severe asthma attacks after receiving treatment with inhaled terbutaline were allocated by double-blind design to receive 1 dose of either 1600 μg budesonide turbohaler or 2 mg/kg prednisolone. The pulmonary index score and peak expiratory flow rate were measured hourly for the first 4 hours. After discharge the children were treated with the same initial doses given 4 times daily, followed by a 25% reduction in dose every second day for 1 week. Parents recorded asthma symptoms and use of β-2 agonists on a daily diary card. Serum cortisol concentration was measured at the end of weeks 1 and 3.**

**Results: Twenty-two children (11 in each group) with similar baseline parameters completed the study. There was a similar improvement in pulmonary index score and peak expiratory flow rate in the 2 groups. Children treated with budesonide showed an earlier clinical response than those given prednisolone, who also showed a decrease in serum cortisol concentration.**

**Conclusion: In children with moderately severe asthma attacks who were treated in the emergency department, a short-term dose schedule of inhaled budesonide turbohaler, starting with a high dose and followed by a decrease over 1 week, is at least as effective as oral prednisolone, without suppressing serum cortisol concentration. (J Allergy Clin Immunol 1998;102:605-9.)**

***Key words:*** *Corticosteroids, budesonide turbohaler, asthma, acute asthmatic attack, children, efficacy, safety*

*Abbreviations used*
ED: Emergency department
PEFR: Peak expiratory flow rate

Corticosteroids have been shown to be effective for the immediate control of acute exacerbation of asthma.[1-5] Intravenous,[1-2] intramuscular,[3] and oral administration of corticosteroids[2,4] have been used with good results, aside from some controversial findings for the intravenous route.[7-8] Oral administration was found to be equally effective to the intravenous route in the initial treatment of acute asthma.[2,9]

Inhaled corticosteroids have greater antiinflammatory and antiasthma potency and fewer systemic effects than oral corticosteroids,[10] and they are delivered directly into the lung. Therefore they are excellent candidate agents for controlling acute asthma. Some recent studies have investigated the effect of inhaled corticosteroids in the exacerbation of asthma,[11-14] but their role in acute asthma and the preferred dose schedule for controlling acute attacks in children have not been established.

Our outpatient asthma clinic has been using inhaled budesonide for this purpose since 1985.[15] In a recent preliminary study, all asthmatic children (aged 0.5 to 16 years), treated in our outpatient asthma clinic with inhaled budesonide over a 1-year period (1996), were evaluated. After participating in an asthma education session, the parents were instructed to initiate treatment with inhaled budesonide at the first sign of an asthma attack, followed by a rapid decrease in dose over 4 to 8 days according to the following schedule: the first or second day (depending on severity of attack), 200 to 400 μg inhaled budesonide 4 times daily, (according to severity) preceded by inhaled β-2 agonists; after the first day or 2, same treatment 3 times daily; for the following day or 2, only inhaled budesonide 200 μg 3 times daily; for the final day or two, inhaled budesonide 200 μg twice daily. Of the 193 children studied, 43 were excluded for noncompliance during the entire follow-up period. The 150 children evaluated had 1061 episodes of asthma over a total cumulative follow-up time of 239 years. The chil-

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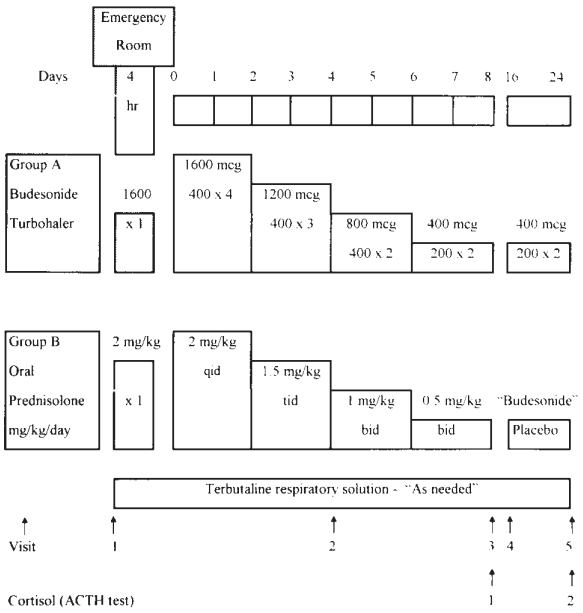


**FIG 1.** Study design: emergency group.

dren were able to control 94% of these attacks using our treatment schedule. Clinical improvement was achieved within a mean of 1.8 ± 0.7 days of treatment, regardless of the age of the child or the type of inhaler/spacer device used. We believe that most of the clinical effect was attributable to the inhaled corticosteroids because, in most of the cases, the children did not control their attacks by β2 agonists alone. This dose schedule was very effective in controlling exacerbation of asthma in asthmatic outpatients with mild-to-moderate asthma; the aim of this study was to consolidate our experience in children who were treated in the emergency department (ED) with more severe asthmatic attacks. Using a double-blind design we compared the efficacy and safety of treatment with inhaled corticosteroids and the treatment with oral steroids in children with moderately severe asthma attacks who were treated on an emergency basis.

## METHODS

The study population included children aged 6 to 16 years with well-diagnosed asthma who were treated in the ED with a moderately severe acute asthma attack, defined by a peak expiratory flow rate (PEFR) of 35% to 75% of predicted values and a pulmonary index score[4] of 8 to 13 (maximal score, 15). Other prerequisites were the ability to correctly operate the turbohaler; the absence of acute febrile illness; freedom from regular treatment with antiasthma controller drugs including inhaled corticosteroids, cromolyn, nedocromil, and theophylline for at least 2 weeks before the study; and not having been treated with oral corticosteroids in the present asthma attack. The hospital's Helsinki Committee approved the study, and parents of all participating children signed informed consent forms.

On admission to the ED, demographic data, past asthma status, and family history (first-degree relatives) of asthma and allergy were recorded. Present asthma status was evaluated by physical examination, including PEFR, oxygen saturation, respiratory rate, inspiratory-expiratory ratio, use of accessory muscle, and presence of wheezing. These factors were rated on a 4-point scale (0, no symptoms, to 3, severe symptoms) to calculate the pulmonary index score (Table I). The children received β2 agonists, administered by nebulization of 5-mg terbutaline respiratory solution (0.5 mL) in 2 mL of 0.9 % saline solution or by 1 puff of 0.5 mg/dose terbutaline turbohaler. Thereafter they were allocated in a double-blind design to receive either a single dose of budesonide turbohaler 1600 μg (4 puffs of budesonide, 400 μg/puff) or prednisolone tablets 2 mg/kg (maximum dose, 60 mg). Patients continued to be monitored hourly for the next 4 hours, with repeated measurements of the PEFR and the pulmonary index score.

Those who responded well to treatment were discharged from the ED with instructions to continue treatment at home (as randomized in the ED), with either tablets of prednisolone 2mg/kg/day and "budesonide turbohaler" (placebo) 1 puff 4 times daily, or budesonide turbohaler 200 μg and "prednisolone tablets" (placebo) 4 times daily. Every second day the dose of both drugs was reduced by 25% (Fig 1). From the eighth day, the children treated with turbohaler continued to receive 200 μg inhaled budesonide twice daily for the next 2 weeks, and those treated with prednisolone received placebo budesonide twice daily for the same period. During the entire study, the children were allowed to use terbutaline turbohaler as rescue medication as needed provided they kept a careful record of the number of puffs used.

The parents were asked to maintain daily diary cards, on which they were to note all events of wheezing and diurnal and nocturnal cough and to rate these symptoms on a 4-point scale, from 0 (no symptoms) to 3 (severe symptoms). The numbers of doses of terbutaline turbohaler used were also recorded. Follow-up visits were scheduled on days 4, 8, 16, and 24, at which time the diary cards were evaluated and PEFR was measured. Serum cortisol concentration, both (fasting) at 8 AM and 1 hour after ACTH stimulation (intravenous Synacten 0.25 mg), was measured in 2 occasions: immediately after the first treatment week on day 8 (to evaluate the influence of active treatment with oral and inhaled steroids) and at the end of the study (day 24), 2 weeks after cessation of oral corticosteroids in the oral prednisolone group or 2 weeks after additional treatment with inhaled budesonide (200 μg twice daily) in the budesonide group.

**TABLE I.** Pulmonary index score

| Score | Respiratory rate | Wheezing | Inspiratory/ expiratory ratio | Accessory muscle use | Oxygen saturation |
|---|---|---|---|---|---|
| 0 | >20 | None | 2:1 | None | 99-100 |
| 1 | 21-35 | End expiration | 1:1 | + | 96-98 |
| 2 | 36-50 | Entire expiration | 1:2 | ++ | 93-95 |
| 3 | >50 | Inspiration and expiration | 1:3 | +++ | <93 |

Compliance was evaluated by counting the number of prednisolone/placebo tablets used and the number of puffs of budesonide/placebo used. The number of puffs was determined by turning the grip of the used turbohaler forward and back until the red mark was seen in the indicator window. If compliance was below 80%, the patient was excluded from the analysis.

## Statistical analysis

The treatment groups were compared for demographic and clinical parameters at baseline. Frequency counts were analyzed with the chi-squared goodness of fit or the Fisher exact test. Differences between mean values for variables that were normally or near-normally distributed (eg, age) were analyzed with the independent Student's *t* test. Differences between mean values for variables that were highly abnormally distributed (eg, number of asthma exacerbations) were analyzed with the Mann-Whitney *U* test or Wilcoxon rank sum test. Comparisons of changes over time within the ED subgroups were conducted by ANOVA with repeated measures using the SAS General linear modules procedure. Weekly means of the groups for symptoms and use of β2 inhalator were compared with ANOVA. All tests were two-tailed, and *P* values of .05 or less were considered significant.

## RESULTS

Twenty-four children who were treated in the ED with an acute asthma attack started the trial; 1 child was later excluded because of pneumonia, and another for noncompliance. Of the 22 children who completed the study, 11 were treated with inhaled budesonide and 11 with oral prednisolone. The 2 groups were similar for demographic parameters, asthma morbidity in the 3 months preceding the study, and asthma status after the onset of the index asthma attack (Table II).

There were no significant differences between the groups in mean PEFR and pulmonary index score or any of its components at the beginning of treatment. At 4 hours, PEFR improved to the same degree ($P < .01$) in both groups, as did the pulmonary index score ($P < .001$; Fig 2). Both groups showed a significant improvement in wheezing ($P < .05$), accessory muscle use ($P < .001$), and oxygen saturation ($P < .05$) and a decrease in respiratory rate and inspiratory-expiratory ratio. All the children were discharged home from the ED.

Day-by-day analysis of asthma symptoms during the first week after discharge showed a better clinical response in the budesonide group, with a significant intergroup difference in diurnal cough on day 1 ($P < .05$) and nocturnal cough on day 2 ($P < .02$; Fig 3). During this week children in both groups rarely used β2 agonists. After day 4 to 5, coughing and wheezing were minimal in both groups. On days 16 and 24, asthma symptoms were similarly mild in both groups.

The compliance rate was 94% in the first study week and 86% during the 2 additional follow-up weeks.

Serum cortisol concentrations at the end of the first treatment week were significantly decreased in almost all the children who were receiving oral prednisolone at both 8 AM (mean, 121 vs 300 nmol/L; $P = .0003$) and 1 hour after stimulation with ACTH analogue (mean, 333 vs 669 nmol/L; $P < .00001$). Two weeks later both groups showed similar normal concentrations (Fig 4).

## DISCUSSION

International guidelines on asthma management recommend a short course of 1 to 2 mg/kg/day of oral or intravenous prednisolone with β2 agonists for the treatment of acute severe asthma.[16-17] Some studies have found that a single administration of high-dose intravenous[6] or oral[4,18] corticosteroids is also effective in controlling acute asthma attacks within 4 hours in both adults[6] and children.[4,18] This was not confirmed by others.[7,8] Barnett et al[9] reported that 2 mg/kg oral methylprednisolone was as effective as 2 mg/kg intravenous methylprednisolone for acute attacks in children. In this study we showed that children with moderately severe asthma attacks who were treated in the ED responded equally well to 1600 μg of inhaled budesonide as to 2 mg/kg oral prednisolone within 4 hours. Engel et al[11] reported similar results in adult outpatients with chronic stable asthma. However, during the first treatment week with decreasing doses, inhaled budesonide improved asthma symptoms significantly faster than oral prednisolone. In an earlier double-blind study by our team, 42 children received either a high starting dose of 2000 μg/day budesonide respiratory suspension (twice daily) followed by a 25% decrease in dose every second day for 1 week or continuous treatment with 500 μg/day. The group with the high starting dose showed significant early clinical improvement from day 2 of treatment without a change in serum cortisol concentration, whereas the other group achieved a comparable improvement only after day 6.[19] Zora et al[20] showed that a 5-day course with up to 2 mg/kg/day of prednisolone produces a transient suppression of the pituitary-adrenal axis. In our study, 8-day treatment with oral prednisolone caused a significant suppression of serum cortisol concentration both fasting at 8 AM and 1 hour after ACTH stimulation, in almost all the children so treated. Because this transient suppression was absent in the children given inhaled budesonide, inhaled budesonide is a safer mode of treatment than oral steroids.

The preferred dose schedule for controlling acute asthma attacks in children has not been established. Connet and Lenney[12] showed that the administration of 1600 to 3200

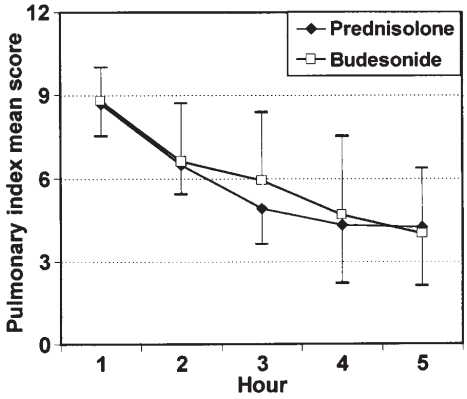


**FIG 2.** Change in total pulmonary index score in the 4 hours immediately after onset of treatment (mean ± SD).

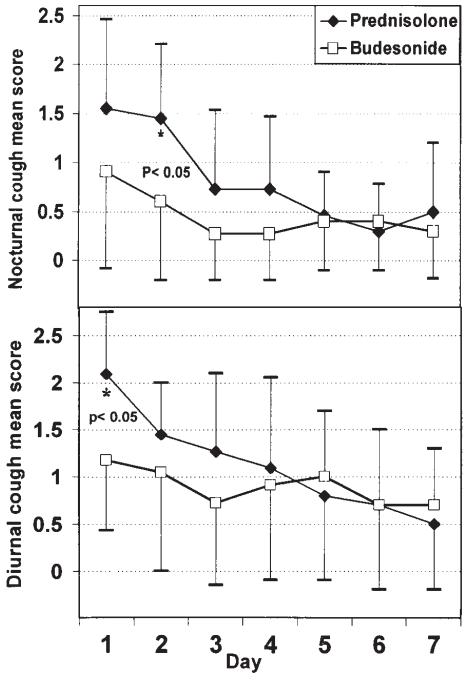


**FIG 3.** Day-by-day analysis of asthma symptom scores during the first week after discharge from the ED (mean ± SD).

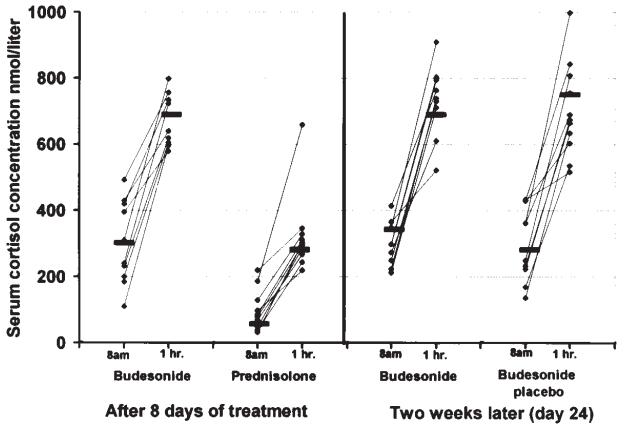


**FIG 4.** Serum cortisol concentration in the budesonide and prednisolone groups at 8 AM (fasting) and 1 hour after stimulation with ACTH analogue.

μg/day of inhaled budesonide for up to 7 days modestly alleviated the severity of wheezing in preschool children in whom asthma had developed after a viral respiratory infection. Sverdymyr et al[13] found that 800 μg budesonide for 3 days with a stepwise decrease every 3 days to 600 μg/day and then 400 μg/day, only attenuated the exacerbation of asthma induced by acute upper respiratory infection. Wilson and Silverman[14] showed that intermittent high-dose inhaled beclomethasone (2250 μg/day every day for 5 days) was beneficial in modifying the severity of acute episodic asthma in school-aged children who were able to use a spacer device. The present trial demonstrated that in an emergency setting, smaller doses of budesonide and a shorter treatment period are effective and safe in controlling moderately severe asthma attacks in children.

We suggest that the effect shown in this study was mainly due to inhaled corticosteroids or oral prednisolone and that the additional effect of the β2 agonist was limited. All the children were admitted to the ED because of a failure to control their attacks by β2 agonists alone given at a mean of almost 3 inhalations in the 24 hours before admission, with the last inhalation approximately 5 to 8 hours before admission. The effect of steroids was also critical during the first 8 days of treatment, when β2 agonists were used only rarely (Table II). The present study focused on the efficacy of inhaled corticosteroids in patients not receiving regular treatment in the 2 weeks preceding the index asthma attack. We know from our preliminary study with 150 outpatients, reported briefly in this article, that the findings for children treated regularly with inhaled budesonide were similar.

**TABLE II.** Demographic data and asthma status in the 2 groups

| | Budesonide | Prednisolone | *P* |
|---|---|---|---|
| Children (no.) | 11 | 11 | |
| Sex | | | |
| Male | 8 | 7 | |
| Female | 3 | 4 | |
| Age (yrs; mean ± SD) | 8.4 ± 3.3 | 10.5 ± 2.7 | NS* |
| Asthma in family (no. of children) | 8 | 8 | NS† |
| During the 3 months before the study (mean ± SD) | | | |
| Asthma attacks (no.) | 2.0 ± 1.8 | 1.9 ± 1.5 | NS‡ |
| ED visits (no.) | 0.3 ± 0.4 | 0.4 ± 0.5 | NS‡ |
| Time (mean ± SD) | | | |
| From onset of present asthma attack (hrs) | 35 ± 19 | 35 ± 32 | NS‡ |
| From *first* β2 agonist inhalation (hrs) | 25 ± 19 | 28 ± 31 | NS‡ |
| From *last* β2 agonist inhalation (hrs) | 5 ± 3 | 8 ± 13 | NS‡ |
| β2 agonist inhalations before onset of trial (no.; mean ± SD) | 2.9 ± 2.7 | 2.4 ± 1.2 | NS‡ |
| Days with β2 use during the first 8 days of treatment (no.; mean ± SD) | 1.6 + 0.8 | 1.2 + 1.1 | NS‡ |

*Student's *t* test.
†Chi-squared test.
‡Wilcoxon rank sum test.

We performed this study to consolidate our previous experience with outpatients who are able to control most of their acute asthma attacks using inhaled budesonide. We believe the main indication for the inhaled corticosteroids is a mild or moderate acute attack at home. However, in children who are able to operate a turbohaler, inhaled budesonide can also be very useful at the onset of moderately severe attacks (before the PEFR drops below 60% of expected and the pulmonary index score rises above 13/15), preceded by inhalation of β2 agonists. The relatively low cost and convenience of administration of oral steroids must also be taken into consideration in choosing the most appropriate regimen for the individual patient but must be weighed against the much higher safety of inhaled budesonide. Although there was some significant difference in the symptom scores in favor of the budesonide turbohaler, we concluded that the treatment with inhaled budesonide was as effective as oral prednisolone. On the basis of our experience, we strongly believe in the effectiveness of this protocol, which is similar to the one we use in our outpatients. To ensure compliance, however, this protocol should always be accompanied by comprehensive patient and parent education of when and how to use the drugs with the inhalers/spacers.

In conclusion, this study shows that in children with moderately severe asthma attacks who were treated in the ED, a short-term dose schedule of inhaled budesonide given by means of turbohaler, starting with a high dose and followed by a rapid decrease in dose over 8 days, is at least as effective as oral prednisolone treatment without the suppression of serum cortisol levels.

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