

## A COMPARISON OF INHALED FLUTICASONE AND ORAL PREDNISONE FOR CHILDREN WITH SEVERE ACUTE ASTHMA

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### ABSTRACT

**Background** Inhaled corticosteroids are effective in the treatment of children with asthma. It is uncertain how inhaled corticosteroids compare with oral corticosteroids in the management of severe acute disease.

**Methods** We performed a double-blind, randomized trial involving 100 children five years of age or older who had severe acute asthma (indicated by a forced expiratory volume in one second [FEV<sub>1</sub>] that was less than 60 percent of the predicted value) and in whom the results could be evaluated. All were treated with an aggressive bronchodilator regimen and received one dose of either 2 mg of inhaled fluticasone through a metered-dose inhaler with a spacer or 2 mg of oral prednisone per kilogram of body weight. They were assessed hourly for up to four hours.

**Results** The mean ( $\pm$ SD) base-line FEV<sub>1</sub> as a percentage of the predicted value was  $46.3 \pm 12.5$  in the fluticasone group (51 subjects) and  $43.9 \pm 9.9$  in the prednisone group (49 subjects). The FEV<sub>1</sub> increased by a mean of  $9.4 \pm 12.5$  percentage points in the fluticasone group and by  $18.9 \pm 9.8$  percentage points in the prednisone group four hours after therapy ( $P < 0.001$ ). None of the children in the prednisone group had a reduction in FEV<sub>1</sub> as a percentage of the predicted value from base line to four hours, as compared with 25 percent of those in the fluticasone group ( $P < 0.001$ ). Sixteen (31 percent) of the children treated with fluticasone were hospitalized, as compared with five (10 percent) of those treated with prednisone ( $P = 0.01$ ).

**Conclusions** Children with severe acute asthma should be treated with oral prednisone and not with inhaled fluticasone or a similar inhaled corticosteroid. (N Engl J Med 2000;343:689-94.)

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**A**CUTE asthma is the most common medical emergency in children. Adequate oxygenation, frequent use of aerosolized  $\beta_2$ -adrenergic agonists, and anticholinergic drugs and systemic corticosteroids are the mainstay of therapy for severe disease.<sup>1-3</sup> Systemic corticosteroids can decrease rates of hospitalization among patients with acute asthma,<sup>4,5</sup> although this finding is not universal.<sup>6,7</sup> Oral corticosteroids decrease the need for hospitalization within four hours after therapy in children treated in the emergency department,<sup>3</sup> shorten the duration of the hospital stay, and prevent the progression of symptoms in outpatients.<sup>8-13</sup>

However, there is concern about the safety of repetitive courses of systemic corticosteroids.<sup>14-16</sup> Many children therefore receive inhaled corticosteroids during acute exacerbations of asthma. The efficacy of inhaled corticosteroids in the treatment of severe acute asthma in children is not known. In a study of children with severe asthma, Scarfone et al.<sup>17</sup> found that 1.5 mg of nebulized dexamethasone per kilogram of body weight was similar in efficacy to 2 mg of oral prednisone per kilogram when evaluated within four hours after administration in the emergency department. Because of the wide age range among the subjects, the authors could not examine pulmonary function as an outcome. Nebulized dexamethasone has systemic effects that may have contributed to its efficacy.<sup>17</sup> In a study in adults, Rodrigo and Rodrigo<sup>18</sup> found that inhaled flunisolide was superior to placebo for severe acute asthma. However, a comparison with systemic corticosteroids was not undertaken. Other studies in adults have enrolled patients with relatively mild asthma<sup>19</sup> or have evaluated primarily the subacute phase of the disease.<sup>20</sup>

Fluticasone propionate is a highly potent inhaled corticosteroid with an oral bioavailability of less than 1 percent<sup>21</sup> and twice the potency of beclomethasone dipropionate in the control of chronic asthma.<sup>22-24</sup> It has fewer systemic effects than beclomethasone in equipotent doses.<sup>22,24-27</sup>

We conducted a study to compare the efficacy of 2 mg of inhaled fluticasone delivered by a metered-dose inhaler with a valved holding chamber (the spacer) with that of 2 mg of prednisone per kilogram as evaluated within four hours after administration in children five years or more of age who were treated in the emergency department for severe acute asthma.

### METHODS

#### Subjects

One of two trained study nurses was notified about children with acute asthma who were seen between 8 a.m. and 9 p.m. in the emergency department of our hospital from October 1995 to April 1999. Children were eligible if they were at least five years old, if the base-line forced expiratory volume in one second (FEV<sub>1</sub>),

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expressed as a percentage of the predicted value, was less than 60, and if they were able to use an inhaler and undergo pulmonary-function tests reliably. Excluded were children with first wheezing episodes who had not previously received bronchodilator therapy, children who required immediate therapy with intravenous corticosteroids or intubation, children who had taken oral prednisone within seven days of the visit, children taking 1000  $\mu\text{g}$  or more of inhaled beclomethasone dipropionate or budesonide per day or 500  $\mu\text{g}$  or more of inhaled fluticasone per day, and children with concurrent cardiopulmonary disease, immunodeficiency, diabetes mellitus, allergy to corticosteroids, or exposure to varicella within the previous 21 days. The study was approved by the Human Ethics Review Board of our institution, and parents provided written informed consent. A log of patients who were missed or excluded or whose parents refused participation was kept so that we could assess the generalizability of the study.

### Study Design

After informed consent had been obtained, eligible children were randomly assigned in a double-blind, double-dummy fashion to receive either a single dose of fluticasone (2 mg; Flovent, Glaxo Wellcome, Mississauga, Ont., Canada) through an inhaler and spacer with a mouthpiece (AeroChamber, Trudell Medical, London, Ont., Canada) or oral prednisone syrup (2 mg per kilogram; maximum, 60 mg; Deltasone, Upjohn Pharmaceuticals, Don Mills, Ont., Canada). All patients received 0.15 mg of nebulized albuterol (Ventolin, Glaxo Wellcome) per kilogram through a jet nebulizer (Whisper Jet Intec, Marquest Medical Products, Englewood, Colo.) with a tight-fitting face mask and an oxygen flow of 6 to 7 liters per minute within 20 minutes before the experimental therapy, at base line (i.e., immediately after the experimental therapy), and 20, 40, 60, 80, and 140 minutes after the experimental therapy. Ipratropium bromide (Atrovent, Boehringer Ingelheim, Burlington, Ont., Canada) at a dose of 250  $\mu\text{g}$  was added to the initial three nebulized doses of albuterol. The placebo inhalers were prepared by Glaxo Wellcome, and the oral syrup placebo was prepared by our pharmacy. They were indistinguishable from the active drugs with respect to appearance, taste, and smell.

Children discharged to their homes after the four-hour period whose parents had agreed to a return visit continued to receive fluticasone or prednisone according to their random assignment (the home phase of the study). Those in the fluticasone group received 500  $\mu\text{g}$  of fluticasone twice daily by inhaler with a spacer and placebo syrup for seven days, whereas the prednisone group received placebo inhaler and 1 mg of oral prednisone per kilogram per day (maximum, 40 mg per day) for seven days. All patients also received albuterol through an inhaler and spacer (0.3 puff per kilogram per dose [100  $\mu\text{g}$  per puff; maximum, 8 puffs per dose]) four times daily for seven days.<sup>28</sup> On day 8, the patients returned for clinical assessment by a physician and pulmonary-function measurements made by the same research nurse who had performed the initial measurements. The research pharmacist assessed compliance with the assigned therapy by weighing the inhalers and by measuring the volume of syrup before and after the study.

### Delivery of Experimental Therapy

In order to maximize the likelihood that the inhaled drugs would be uniformly distributed throughout the lungs, all children received the first dose of nebulized albuterol and ipratropium immediately before the experimental therapy. The experimental treatment consisted of eight puffs of fluticasone, containing 250  $\mu\text{g}$  of drug per puff, or equivalent placebo given through an inhaler and spacer with a mouthpiece. A deep-inhalation technique was used, with five seconds of breath-holding after each actuation.<sup>29</sup> The inhaler was shaken after each actuation. This technique was also used in the home phase of the study. Children who vomited within 20 minutes after swallowing the syrup received a repeated dose; further vomiting necessitated withdrawal from the study.

### Randomization

A blocked randomization code was prepared by our pharmacy from a computer-generated list of random numbers. The pharmacy prepared sequential sealed packets containing the study drugs. The randomization code was revealed only after all the patients had completed the study.

### Other Treatments and Follow-up

The patients' attending physicians were requested not to administer corticosteroids unless the patient was in marked respiratory distress or needed hospitalization after the four-hour study period. All decisions about further treatment and hospitalization were made by the attending physicians, who were not involved in the study and were unaware of the outcome data. Children in persistent, clinically significant respiratory distress 4 or 5 hours after the experimental intervention were hospitalized; the others were discharged either immediately or after up to 12 hours of further treatment in the emergency department.

The parents of all enrolled patients were telephoned by the study nurses within 72 hours after the children's discharge and on day 15 to ascertain whether the children had had a relapse or had been hospitalized.

### Outcome Measures

The change in FEV<sub>1</sub> as a percentage of the predicted value from base line (time 0) to 240 minutes was the primary outcome measure. Secondary outcomes were the changes in the forced vital capacity (FVC) and the predicted peak expiratory flow rate as percentages of the predicted values, the respiratory rate, transcutaneous oxygen saturation while the child was breathing room air (measured with a Nellcor Saturation Monitor, Nellcor-Mallinckrodt, Montreal), and the rate of hospitalization. Lung-function measurements were made with a portable spirometer (Roxon Mediatech, Montreal) according to the recommendations of the American Thoracic Society.<sup>30</sup> After initial teaching of the patients by the research nurse, the spirometric variables were measured in sets of six and expressed as percentages of predicted values for height and sex.<sup>31</sup> The highest value was accepted for analysis. These outcomes were measured at -20 minutes (before the initial nebulized dose of study medication); at 0 minutes (before the experimental therapy); at 60, 120, 180, and 240 minutes; and on day 8.

### Statistical Analysis

The sample size was based on an estimated standard deviation of 15 for the change in the percentage of the predicted FEV<sub>1</sub> in the prednisone group. In order to allow detection of a 10 percentage point difference between the groups in the degree of improvement in FEV<sub>1</sub> (as a percentage of the predicted value) from base line to 240 minutes and to maintain an  $\alpha$  error of 0.05 and a  $\beta$  error of 0.10, the required size of the sample was 94 children.

Differences between the two drug regimens were tested with use of Student's *t*-test for continuous and normally distributed variables and with use of the Wilcoxon rank-sum test for variables with a skewed distribution.<sup>32</sup> The distribution of ordered variables was compared by means of the Mantel-Haenszel chi-square test,<sup>33</sup> and the Cochran-Mantel-Haenszel chi-square test was used for stratified analyses.<sup>33</sup> Binary variables were examined with Fisher's exact test.<sup>33</sup> The change in pulmonary-function values over time was analyzed by means of mixed-model regression, which incorporated repeated observations of individual patients. This method requires an assumption to be made about the complex covariance associated with repeated measurements over time.<sup>34</sup> We assumed an autoregressive covariance structure in which observations closer together in time are more correlated than those further apart. A quadratic time variable was added to test for nonlinearity. Data on all patients, including those with missing values at one or several times, were included in the model. The values and their standard deviations were estimated by the Proc Mixed program (SAS Institute, Cary, N.C.).<sup>35</sup> All statistical tests were two-tailed.

## RESULTS

## Characteristics of the Patients

Between October 1995 and April 1999, 8001 children were seen in our emergency department who had a discharge diagnosis of asthma. Of these, 2084 were excluded because the research nurses were not present when they were evaluated, 5196 because they were too young, 264 because they could not perform spirometry reliably, and 73 because they had already been enrolled in this study. Also excluded were 160 children who were taking prednisone and 76 who were taking high-dose inhaled corticosteroids before arrival. The parents of 45 children refused permission for them to participate. One hundred three children were randomly assigned to active therapy: 52 to the fluticasone group and 51 to the prednisone group. One child in the prednisone group repeatedly vomited after being given the experimental syrup; one child in the fluticasone group was subsequently excluded because his FEV<sub>1</sub> reached 92 percent of the predicted value after the first nebulized treatment and experimental therapy was subsequently not given; and one child became acutely ill within one hour after treatment with prednisone, necessitating admission to the intensive care unit.

Of the 100 children who were able to proceed with spirometry, 51 were in the fluticasone group and 49 in the prednisone group. Two patients in the fluticasone group required intravenous hydrocortisone at two hours because of increasing respiratory distress and did not complete the study. Despite respiratory improvement, two other children (one in each group) were unable to undergo pulmonary-function testing at 240 minutes because of fatigue and nausea.

There were no significant demographic or clinical differences between the two groups, except for sex (Table 1). Among the 79 patients discharged to their homes, the families of 31 declined to participate in the home phase of the study because of reluctance to make a return visit, 8 were excluded because they had respiratory distress or vomiting requiring treatment with systemic corticosteroids or intravenous hydration at discharge, and 1 patient did not return. Of the 39 children who completed the home phase, 13 were in the fluticasone group and 26 in the prednisone group.

## Pulmonary Function

The improvements in FEV<sub>1</sub>, FVC, and predicted peak expiratory flow rate from base line (time 0) to 240 minutes were significantly greater in the prednisone group than in the fluticasone group (Table 2). Specifically, the FEV<sub>1</sub> increased by a mean of 9.4±12.5 percentage points in the fluticasone group and by 18.9±9.8 percentage points in the prednisone group four hours after therapy (P<0.001). The difference in the degree of change in the FEV<sub>1</sub> as a percentage of

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY GROUPS.\*

CHARACTERISTIC	FLUTICASONE GROUP (N=51)	PREDNISONE GROUP (N=49)
Age (yr)		
Mean	9.3±3.3	9.5±3.2
Range	5–17	5–17
Sex (M/F)†	25/26	34/15
Mean duration of attack (hr)	43.6	43.3
Mean hospitalizations for asthma in previous year (no.)	0.44	0.24
History of atopy (%)		
Personal	54.9	55.1
Family	68.6	71.4
Currently using inhaled corticosteroids (no.)		
Beclomethasone dipropionate	19	20
Budesonide	4	3
Fluticasone propionate	4	2
Lung-function test results (% of predicted value)‡		
FEV <sub>1</sub> at –20 min	35.8±8.5	34.4±9.8
FEV <sub>1</sub> at 0 min	46.3±12.5	43.9±9.9
FVC at 0 min	50.6±15.9	47.6±12.6
PEFR at 0 min	45.0±15.1	40.7±13.2
Oxygen saturation at 0 min (%)	95.3±2.3	95.4±2.0
Respiratory rate at 0 min (breaths/min)	31.8±8.0	29.9±6.2

\*Of 103 children who were randomly assigned to treatment, 3 were not included in the analysis because of inability to tolerate prednisone, recovery of forced expiratory volume in one second (FEV<sub>1</sub>) after pretreatment, or acute illness within one hour after treatment. Plus-minus values are means ±SD.

†P=0.044 for the difference between the groups.

‡FVC denotes forced vital capacity, and PEFR peak expiratory flow rate.

the predicted value from –20 to 240 minutes was also significant (P=0.002). All the mixed models for pulmonary-function tests included a significant coefficient for a quadratic time effect, since the improvement in pulmonary function slowed after two hours. Furthermore, there was progressive improvement in FEV<sub>1</sub> as a percentage of the predicted value over the study period in the prednisone group, whereas in the fluticasone group no further improvement occurred after three hours (Fig. 1). Adjustment for covariates such as age, sex, FEV<sub>1</sub> at base line, previous hospitalization, or use of inhaled corticosteroids before the study did not significantly alter these findings.

In the prednisone group, 13 of the 49 children (27 percent) had an excellent response (arbitrarily defined a priori as an increase in the FEV<sub>1</sub> expressed as a percentage of the predicted value of at least 25 percentage points from base line to 240 minutes), 32 (65 percent) had a moderate response, and 4 (8 percent) had a poor response (defined as an increase in FEV<sub>1</sub> of less than 5 percentage points). In the fluticasone group, 5 of 51 (10 percent) had an excellent response, and 16 (31 percent) had a poor response (P=0.002). None of the patients taking prednisone

TABLE 2. CLINICAL OUTCOMES WITHIN FOUR HOURS AFTER THERAPY.\*

OUTCOME	FLUTICASONE GROUP (N=51)		PREDNISONE GROUP (N=49)		P VALUE
	BASE LINE	240 MIN	BASE LINE	240 MIN	
FEV <sub>1</sub> (% of predicted value)	46.3±12.5	55.7±16.4	43.9±9.9	62.8±13.1	<0.001†
FVC (% of predicted value)	50.6±15.9	59.6±17.8	47.6±12.6	66.2±15.1	0.008†
PEFR (% of predicted value)	45.0±15.1	52.6±18.7	40.7±13.2	60.7±17.1	<0.001†
Respiratory rate (breaths/min)	31.8±8.0	29.1±7.2	29.9±6.2	27.8±5.7	0.86‡
Oxygen saturation (%)	95.3±2.3	95.5±2.2	95.4±2.0	96.0±1.8	0.14‡
Adverse events (no. of patients)					
Vomiting		24		8	0.001
Tremor		17		6	0.017
Intravenous hydration required		9		0	0.003

\*FEV<sub>1</sub> denotes forced expiratory volume in one second, FVC forced vital capacity, and PEFR peak expiratory flow rate. Plus-minus values are means ±SD.

†The P value is for the drug-time interaction in the mixed model, including drug, time, and the square of time (the quadratic time effect).

‡The P value is for the comparison between groups in the change from base line to 240 minutes, by the Wilcoxon rank-sum test.

had a reduction in FEV<sub>1</sub> from base line to four hours, whereas 25 percent of the patients taking fluticasone did ( $P<0.001$ ).

Among the 39 children who returned on day 8, the FEV<sub>1</sub> as a percentage of the predicted value had improved by 37.6 percentage points from base line for the 13 children in the fluticasone group and by 42.1 percentage points for the 26 in the prednisone group.

#### Hospitalization

The rate of hospitalization after the study was higher in the fluticasone group (31 percent) than in the prednisone group (10 percent,  $P=0.01$ ) (Table 3). The results remained significant after adjustment for sex and previous hospitalization (data not shown). Five of the 35 patients in the fluticasone group who were discharged and 2 of the 44 such patients in the prednisone group were given oral corticosteroids before leaving the emergency department. Two children were admitted to the intensive care unit, one from each group. None of the children who were initially sent home were subsequently hospitalized.

#### DISCUSSION

In our trial of therapy for children with severe acute asthma, the degree of improvement in pulmonary function in the initial four hours among those treated with prednisone was about twice that in those given fluticasone. Furthermore, the rate of hospitalization in the fluticasone group was about three times that in the prednisone group.

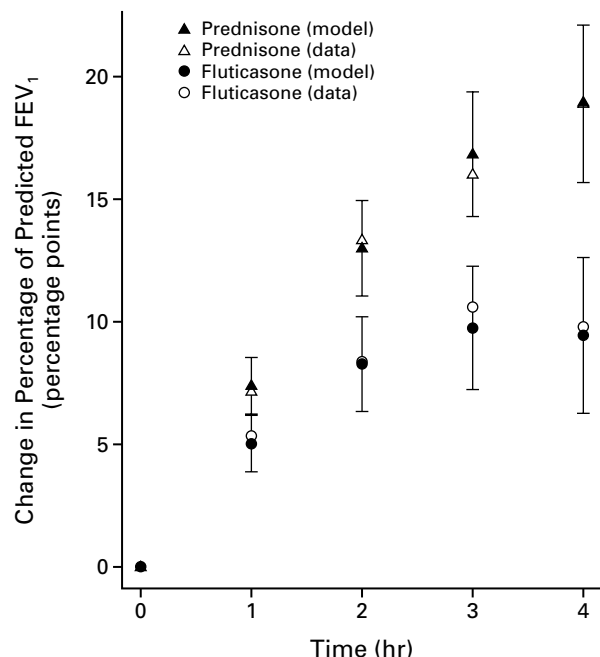
Several studies have demonstrated a significant benefit of corticosteroids from two to four hours after administration in patients with asthma.<sup>3,7,17,18,36</sup> The proposed biologic mechanisms include up-regulation

of  $\beta_2$ -adrenergic receptors, mucosal vasoconstriction, and a decrease in airway edema.<sup>37,38</sup>

Scarfone et al.<sup>17</sup> found that oral prednisone and nebulized dexamethasone had similar efficacy in the emergency treatment of children with asthma. In contrast to fluticasone, dexamethasone is active systemically, because it is not metabolized on the first pass through the liver.<sup>17</sup> The absorption of dexamethasone was further enhanced by the nebulization process, which resulted in a higher rate of oropharyngeal deposition of the drug.<sup>29</sup> Less than 1 percent of fluticasone is absorbed from the gastrointestinal tract,<sup>21</sup> with correspondingly weaker systemic effects. Rodrigo and Rodrigo<sup>18</sup> found in a placebo-controlled trial that adults taking inhaled flunisolide had better lung function than those taking placebo. The dose of flunisolide was high, and the treatment was given frequently over a three-hour period.

In our study, a possible reason for the poorer outcome in the fluticasone group may have been suboptimal delivery of the drug into the lung because of severe airway narrowing. We attempted to minimize this possibility by choosing a high dose of fluticasone, by administering pretreatment with nebulized bronchodilators, by using an inhaler with a mouthpiece, and by using a deep-inhalation technique. Nevertheless, airways blocked by mucus would receive less inhaled fluticasone, whereas systemic corticosteroids would be delivered to any area with a blood supply. The fact that there was no further improvement after three hours in the fluticasone group may indicate the maximal effect of the  $\beta_2$ -adrenergic agonist.

Age did not have a significant effect on the difference in efficacy between the two treatments, which suggests that the potentially suboptimal cooperation



**Figure 1.** Change in Forced Expiratory Volume in One Second (FEV<sub>1</sub>) as a Percentage of the Predicted Value over Time in the Two Groups.

Values shown are fitted means from the regression model, minus the intercept for each group, with 95 percent confidence intervals. Solid symbols show the means calculated from the model, and open symbols show the means of the actual data. The values for prednisone overlap at four hours.

with testing and effort of younger children did not have a major role. Likewise, adjustment for base-line FEV<sub>1</sub> did not affect the results. Since our entire study group consisted of children with severe disease, they may have had too much acute inflammation and mucous plugging to be successfully treated with inhaled corticosteroids.

In our study, the continuation of therapy after discharge resulted in similar improvement of pulmonary function in the two groups. Youngchaiyud et al.<sup>20</sup> showed that, after initial treatment with prednisolone, therapy with either budesonide or prednisolone for seven days resulted in similar rates of recovery. A study by Levy et al.<sup>19</sup> suggests that adults with mild exacerbations of asthma may be successfully treated with high doses of fluticasone. Studies by Connett and Lenney<sup>39</sup> and by Wilson and Silverman<sup>40</sup> also found a significant symptomatic benefit of high doses of inhaled corticosteroids given to children at the onset of an upper respiratory tract infection and those with the first symptoms of asthma, respectively. In our study, because of the large differences in the rates of hospitalization between the two groups and the small number of patients whose parents agreed

**TABLE 3.** STATUS OF THE PATIENTS AT THE END OF THE STUDY.\*

STATUS	FLUTICASONE GROUP (N=51)	PREDNISONE GROUP (N=49)
	number (percent)	
Hospitalized	16 (31)	5 (10)
Discharged		
After further therapy in emergency department	29 (57)	27 (55)
At 240 min	6 (12)	17 (35)

\*P=0.001 for the comparison of all three status categories. P=0.013 for the comparison between hospitalized patients and all discharged patients. P values were calculated by the Cochran-Mantel-Haenszel chi-square test.

to a return visit, analysis of the home phase was not feasible; any conclusions about this subgroup would therefore be misleading. The results of our study may also not be generalizable to children with mild exacerbations of asthma.

In conclusion, children with severe acute asthma who are treated in the emergency department derive significantly greater benefit from oral prednisone than from inhaled fluticasone. We recommend that inhaled fluticasone or similar inhaled corticosteroids not be used in the management of severe asthma in the emergency department.

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