Comparative efficacy of oral dexamethasone versus oral prednisone in acute pediatric asthma

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Objective: The objective was to determine whether 2 days of oral dexamethasone (DEX) is more effective than 5 days of oral prednisone/prednisolone (PRED) in improving symptoms and preventing relapse in children with acute asthma.

Study design: This was a prospective randomized trial of children (2 to 18 years old) who presented to the emergency department with acute asthma. PRED 2 mg/kg, maximum 60 mg (odd days) or DEX 0.6 mg/kg, maximum 16 mg (even days) was used. At discharge children in the PRED group were prescribed 4 daily doses (1 mg/kg/d, maximum 60 mg); children in the DEX group received a prepackaged dose (0.6 mg/kg, maximum 16 mg) to take the next day. The primary outcome was relapse within 10 days.

Results: When DEX was compared with PRED, relapse rates (7.4% of 272 vs 6.9% of 261), hospitalization rates from the emergency department (11% vs 12%) or after relapse (20% vs 17%), and symptom persistence at 10 days (22% vs 21%) were similar. In the PRED group more children were excluded for vomiting in the emergency department (3% vs 0.3%; P = .008), more parents were noncompliant (4% vs 0.4%; P = .004), and more children missed ≥2 days of school (19.5% vs 13.2%; P = .05).

Conclusion: In children with acute asthma, 2 doses of dexamethasone provide similar efficacy with improved compliance and fewer side effects than 5 doses of prednisone. (J Pediatr 2001;139:20-6)

Asthma accounts for >1.8 million emergency department visits annually, and children account for approximately half of these visits.[1] Suppression and reversal of inflammation is the cornerstone for managing acute symptoms and preventing relapse. Guidelines emphasize the use of a short course of corticosteroids at discharge from the ED to decrease relapse.[2] A common practice is to prescribe a 4- to 5-day course of prednisone/prednisolone to children with asthma exacerbations.

See editorial, p 3.

Despite receiving prescriptions for corticosteroids, 5% to 25% of patients discharged from the ED will have relapse within 3 weeks.[3-11] Admission rates for patients with relapse vary from 50%[3] to 83%[10] and may be affected by patient compliance. Even with short-term medication regimens, 7% to 28% of patients never fill their prescriptions.[12-15] Poor palatability of the medication and a treatment period of several days may further reduce patient compliance.

Dexamethasone is a long-acting corticosteroid that is well absorbed and has been used safely in children with croup. Our hypothesis was that a 2-day course of DEX dispensed from the ED would be well tolerated and superior to a prescribed 5-day course of PRED in improving symptoms and preventing relapse in the 10 days after an acute asthma exacerbation.

DEX	Oral dexamethasone
ED	Emergency department
PEFR	Peak expiratory flow rate
PRED	Oral prednisone/prednisolone

METHODS

Study Population

The study group consisted of children 2 to 18 years old with a known history of asthma (2 or more episodes of wheezing treated with β-adrenergic agonists ± steroids) who presented to the pediatric ED with an acute exacerbation, defined as worsening of their asthmatic symptoms or increased difficulty in breathing with worsening of their peak expiratory flow rates. Children <2 years old were not enrolled to avoid including patients with bronchiolitis.

Children were considered for the study if they required at least 2 albuterol nebulizer treatments in the ED. Informed consent was obtained from the parent or legal guardian, and assent was obtained from the patient, if appropriate.

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Children were excluded for any of the following reasons: reported use of oral corticosteroids in the 4 weeks before the current episode, history of intubation, varicella exposure in the preceding 3 weeks, concurrent stridor, possible presence of an intrathoracic foreign body, chronic respiratory disease (eg, cystic fibrosis), cardiac disease, or the need for immediate airway intervention.

Study Design

This randomized, prospective, clinical trial was approved by the Institutional Review Board of the Eastern Virginia Medical School. The study took place between November 1998 and September 1999 at the ED of a 168-bed tertiary care urban pediatric hospital. To limit potential investigator bias, the ED nursing staff classified the initial severity of an acute asthma exacerbation. Each child's exacerbation was classified as mild, moderate, or severe based either on the percentage of a child's predicted PEFR or an "asthma score." Our asthma scoring system (modified from one published by the National Institutes of Health)[16] rates the severity of an asthma episode according to signs and symptoms and is used to evaluate the degree of respiratory distress in patients who are too young or uncooperative with performing reliable pulmonary function tests. It was validated in 2 previous studies of children with acute asthma.[17,18] Each patient's asthma episode was classified as "mild" if the PEFR was >70% of the predicted value or the asthma score was 5 to 7, "moderate" if the PEFR was 50% to 70% of the predicted value or the asthma score was 8 to 11, or "severe" if the PEFR was <50% of the predicted value or the asthma score was 12 to 15.

PEFR was used to determine asthma severity if the child's effort was considered to be reliable and reproducible and could be obtained throughout the study period; otherwise, the asthma score was used to classify the severity of the exacerbation. The predicted PEFR was determined from normative data for patients of the same height, sex, and race.[19]

All children were treated according to our standard ED asthma treatment protocol. Children received the first 3 albuterol nebulizations at 20-minute intervals (2.5 mg if weight <20 kg or 5 mg if weight >20 kg), and subsequent doses were given as ordered by the physician. Ipatropium bromide (0.5 mg) was added to 2 or 3 of the initial albuterol nebulizations depending on asthma severity. Oral corticosteroids were given with the second dose of nebulized albuterol. Oxygen was administered to maintain the patient's oxygen saturation (measured by pulse oximeter) ≥94%. Children who needed a second dose of albuterol were approached for enrollment in the study.

On odd enrollment days children received oral PRED, and on even enrollment days children received oral DEX. Children in the PRED group received 2 mg/kg; maximum 60 mg of liquid prednisolone (Prelone 15 mg/5 cc) or prednisone USP 10-mg or 20-mg tablets (dose rounded to the nearest 5 mg). The choice between liquid or tablet was based on parental and child preference. If the child vomited the liquid medication, he or she was strongly urged to consider crushed tablets mixed in applesauce or chocolate/vanilla pudding for the subsequent dose. Children in the DEX group received 0.6 mg/kg; maximum 16 mg of dexamethasone USP 4-mg tablets (dose rounded to the nearest 2 mg) given as intact tablets or crushed and mixed in applesauce or chocolate pudding. The dose of either medication was readministered if the patient vomited within 30 minutes of taking it. Those who vomited 2 doses of the steroid were excluded from the study. The child's current asthma medications were recorded. Pulse and respiratory rates, pulse oximeter readings, PEFR, and asthma score were recorded before the first nebulizer treatment and after each subsequent treatment. The total number of nebulizer treatments, patient disposition, and medications at discharge were recorded.

A decision to admit or discharge the child was made by the attending physician based on relief of symptoms, objective improvement in clinical asthma score, PEFR, or both, and the ability to maintain oxygen saturations ≥94% on room air. Only children who were discharged from the ED with corticosteroids were included in the final analysis.

At discharge children in the PRED group were given a prescription for 4 daily doses of prednisone/prednisolone (1 mg/kg/dose; maximum 60 mg/d). Children in the DEX group received a premeasured dose of dexamethasone (0.6 mg/kg; maximum 16 mg) to take at home the next day. Albuterol inhalations were recommended on a 4- to 6-hour basis for the first 2 days after discharge, then as needed. No other asthma medications were to be used during the next 10 days.

The primary outcome measure was the rate of relapse, defined as an unscheduled visit to a medical facility resulting from the patient's or parent's perception of persistent, worsening, or recurrent asthma symptoms in the 10 days after discharge from the ED. Secondary outcome measures were the rate of hospitalization (both initially from the ED and after relapse), frequency of vomiting, reported medication compliance, persistence of symptoms, and school or workdays missed. A research assistant contacted each patient's family 11 to 14 days after the patient was discharged from the ED to obtain follow-up data.

Statistical Analysis

Assuming a baseline relapse rate of 12% and accepting an α of 0.05 and a β of 0.8, a sample size of 250 per group was needed to detect an absolute difference in relapse rate of 5% between the groups.

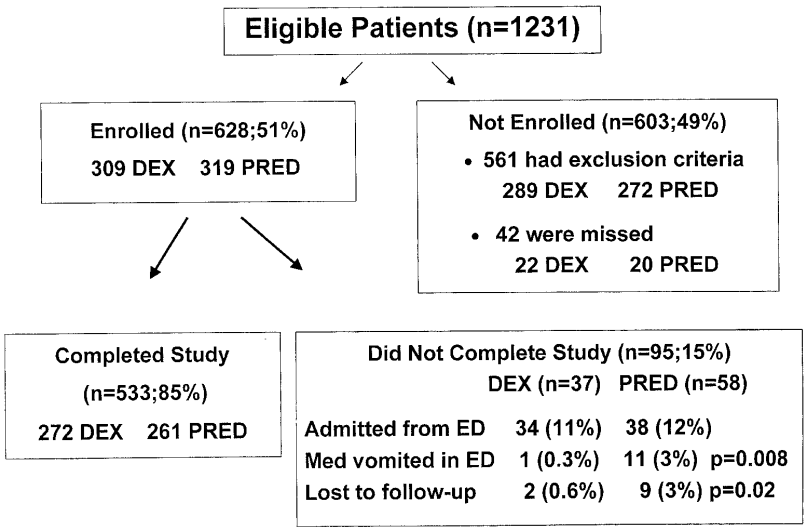

Figure. Patient enrollment data showing number of eligible patients, number of patients who were not enrolled (and reason they were not included), and number of patients who completed this study. Fifteen percent of enrolled patients were subsequently excluded for reasons noted in lower right box.

Table I. Baseline demographic and clinical data

	DEX (n = 272)	PRED (n = 261)	*P* value
Sex			.99
Male (%)	178 (65)	171 (66)	
Female (%)	94 (35)	90 (34)	
Race			.07
White (%)	44 (16)	26 (10)	
Black (%)	219 (81)	229 (88)	
Other (%)	9 (3)	6 (2)	
Age (y)	6 (5,7)	7 (6,7)	.06
Weight (kg)	23.2 (21.7, 26.1)	25.9 (24.5, 29)	.05
Heart rate	124 (119, 126)	119 (116, 122)	.20
Respiratory rate	32 (30, 32)	30 (28, 30)	.07
Pulse oximeter saturation	96 (96, 97)	96 (96, 97)	.71
Previous medications			
β-Agonist (inhaled) (%)	221 (81)	218 (84)	.54
β-Agonist (oral) (%)	10 (4)	4 (2)	.18
Inhaled steroids (%)	52 (19)	36 (14)	.07
Other medications (%)*	21 (8)	22 (8)	.76
Initial asthma severity			.92
Mild (%)	59 (22)	60 (23)	
Moderate (%)	153 (56)	146 (56)	
Severe (%)	60 (22)	55 (22)	

*Cromolyn, antihistamine, decongestant.
Demographic comparisons with the number of children (percentage) shown. Continuous baseline characteristics are presented as median (95% CI). There were no significant differences in any baseline parameter between groups.

The 2 groups were compared by appropriate tests of association. We used Pearson's χ^2 test for dichotomous and ordinal variables, the Student *t* test for equality of means when continuous variables were normally distributed, the Wilcoxon Rank Sum test for equality of medians when continuous variables were non-normally distributed, and Cramer's V test of association for 2 × J tables when J > 2 and data were nominal. All proportions were tested with the 2-sample test of proportions. Logistic regression was used to determine whether there was a relation between study group and relapse. Analysis was conducted with STATA software version 6.0.

RESULTS

Patient enrollment data are shown in the Figure. Patients could be enrolled more than once provided they had not used oral corticosteroids in the 4 weeks before the current episode. Approximately 8% of patients were included more than once. Of the 1231 eligible children, 628 were enrolled and 533 (272 in the DEX group and 261 in the PRED group) completed the study. As shown in the Figure, significantly more enrolled children were excluded for vomiting in the PRED group than in the DEX group (3% vs 0.3%; $P = .008$). The 2 groups were similar in demographic and baseline clinical characteristics, including initial asthma severity (Table I). There were no significant differences between groups in the parents' reported use of inhaled or oral β-adrenergic agonists and inhaled steroids in the 24 hours before the ED visit (Table I).

PEFR was performed on 185 (35%) children. Of these, only 96 children (18% of total; 49 in the DEX group and 47 in the PRED group) had PEFR data that were considered sufficiently reliable to classify initial severity of asthma.

There was no difference between groups in the total number of nebulizer treatments (albuterol ± ipratropium) given in the ED, the total time spent in the ED, or asthma severity at discharge (Table II).

There was no significant difference in relapse rates between the 2 groups (DEX 7.4%; PRED 6.9%; odds ratio 1.08; 95% CI 0.55 to 2.08; $P = .84$)

(Table III). Of those who relapsed, there was no difference in the rate of subsequent admission. An intention-to-treat analysis of relapse rates, assuming that the children who were excluded for vomiting and those who were lost to follow-up all had relapse, favored the DEX group, but the difference was not significant (DEX 24 [8.7%] of 276; PRED 38 [13.5%] of 281; odds ratio 0.61; 95% CI 0.35 to 1.05; $P = .07$).

When stratified by initial asthma severity, the relapse rate was similar between groups. Most relapses occurred in the first 3 days after ED discharge, with the greatest number occurring on day 2 (8 in the DEX group and 6 in the PRED group). There was no significant association between the time to relapse and the type of steroid administered.

A significantly greater number of children in the PRED group missed 2 or more days of school, and more parents in the PRED group reported missing at least 1 day of work. More children reportedly vomited the PRED at home, and significantly more parents in the PRED group reported not giving their child the medication (because the prescription was not filled). This study was designed to compare current outpatient prescribed steroid therapy versus DEX dispensed from the ED. Even though 4% of the parents in the PRED group reported they did not fill the prescription, only 1 of these patients was among the 18 children who had relapse. In a similar fashion, only 1 child in the DEX group who relapsed did not get the steroid. If both these patients are excluded, there is no significant change in the comparative relapse rates between groups.

There was no significant difference between the groups in the prevalence of persistent symptoms (cough, wheeze, chest tightness, night awakening, difficulty in maintaining daily activity) at the time of follow-up (Table III).

Eighty-nine percent (243) of parents in the DEX group believed that the DEX and PRED were comparable in efficacy and that the 2-day regimen of DEX, especially when dispensed from the ED, was much more convenient. Five parents believed that the DEX was not as effective as PRED, and 4 others reported that their child had been more irritable while taking the DEX. The remaining 20 dissatisfied parents in the DEX group had children who had relapsed.

Table II. Clinical course in the emergency department

	DEX (n = 272)	PRED (n = 261)	*P* value
No. of nebulizers in ED	3 (3, 3)	3 (3, 3)	.30
Time in ED (min)	140 (130, 147)	125 (120, 132)	.09
Asthma severity at discharge			
Mild (%)	262 (96)	255 (98)	.35
Moderate (%)	10 (4)	6 (2)	

Data are shown as median (95% CI) or number of children (percentage) within outcome groups. There was no significant difference between groups in any parameter.

Table III. Outcome data

	DEX (n = 272)	PRED (n = 261)	*P* value
Primary outcome			
Relapse rate (%)	20 (7.4)	18 (6.9)	.84
Secondary outcomes			
Admit after relapse (%)	4 (20)	3 (17)	.81
Medication not given (%)	1 (0.4)	10 (4)	.004
Medication vomited at home (%)	6 (2)	11 (4)	.17
Missed ≥2 school days (%)	36 (13.2)	51 (19.5)	.05
Parent missed work (%)	44 (16.2)	59 (22.6)	.06
Persistent symptoms (by history)			
Cough (%)	57 (21.3)	48 (18.7)	.38
Wheeze (%)	32 (12.0)	30 (11.7)	.72
Tightness of chest (%)	11 (4.1)	11 (4.3)	1.0
Night awakening (%)	13 (4.9)	16 (6.2)	.61
Difficulty maintaining daily activity (%)	14 (5.2)	18 (7.0)	.33

Summary of outcomes 10 days after ED visit. Data show number of children (percentage) in each outcome group.

DISCUSSION

This prospective, randomized, clinical trial found that the relapse rate in children with acute asthma was not different when 2 doses of oral DEX (dispensed in the ED) were compared with 5 doses of oral PRED (1 dispensed in the ED and 4 prescribed home doses). There also was no difference in symptom improvement or the rate of hospitalization.

Because corticosteroids improve pulmonary function, reduce the rate of hospitalization, and decrease the relapse rates in patients with acute asthma exacerbations,[5,6,20-25] PRED is recommended by the National Institutes of Health consensus panel for outpatient use after an asthma exacerbation.[2] These relatively short-acting

steroids have a biologic half-life of 12 to 36 hours, necessitating daily dosing of the drug,[26] usually for 4 to 5 days.

Reasons for noncompliance with medications prescribed on discharge from the ED included lack of insurance,[12] insufficient funds,[13] parental noncompliance,[14] cost,[15] and medications prescribed for a course of several days.[27] Although parents knew that we would be monitoring their child, 10 (4%) parents in the PRED group admitted not giving the medication because they failed to fill the prescription. Noncompliance may have been higher, because there were frequent conflicting reports from different caretakers on whether the medicine was ever bought and how many doses were given. The 2 reasons given for not purchasing the PRED were "insufficient funds" (n = 6) and "I forgot" (n = 4). In the DEX group only 1 parent reported not giving their child the second dose of DEX.

Children may vomit or refuse to swallow medication, especially if it is bitter or has to be given in large volumes. A 3% to 15% incidence of vomiting after oral PRED is taken has been reported.[10,28,29] Only those children who vomited both doses of steroids in the ED were used to calculate the incidence of vomiting, accounting for the low incidence compared with previous studies. In our study children given DEX tablets (crushed or whole) vomited less often than those given the PRED liquid or tablets, both in the ED and at home. Since this study was completed, we have used the parenteral formulation of DEX (dexamethasone sodium phosphate injection USP 10 mg/mL) mixed with flavored syrup for younger children, with very good patient acceptance.

To improve compliance and decrease asthma relapse rates, several investigators have studied long-acting parenteral steroid preparations given at discharge from the ED. In a small study (17 patients), a single dose of intramuscular methylprednisolone acetate (80 mg) decreased relapse rates from 20% to 0% compared with a 10-day tapering dose of oral methylprednisolone.[11] In a larger study (56 patients), a larger dose of intramuscular methylprednisolone acetate (240 mg) reduced relapse rates from 31% to 7% compared with placebo.[3] A single dose of triamcinolone acetate (40 mg intramuscularly) produced a relapse rate equal to that of oral PRED (40 mg/d for 5 days),[4] and 1 dose of intramuscular DEX acetate produced similar improvement in symptoms compared with 5 days of oral PRED in 32 children discharged from a pediatric clinic.[27] Repository preparations of corticosteroids (the acetate form of methylprednisolone, triamcinolone, or dexamethasone), however, have a long duration of action (1 to 3 weeks), raising concern for prolonged adrenal suppression, especially if used in repeated doses.[30]

Short-acting DEX phosphate (0.3 mg/kg) intramuscularly or 3 days of oral PRED was used in 42 children presenting to the ED with mild to moderate asthma. No child had a relapse or deterioration of symptoms during the subsequent 5 days.[31]

Based on these studies, we hypothesized that patient compliance and tolerance would be improved with oral DEX rather than PRED in acute asthma. DEX is a potent, long-acting glucocorticoid with a biologic half-life of 36 to 72 hours. It is approximately 6 times more potent than PRED.[26] DEX is well absorbed orally; the relative oral bioavailability of DEX is 70% of that achieved by intramuscular administration.[32,33] Two doses of oral DEX at 0.6 mg/kg/dose should be pharmacologically equivalent to 5 days of oral PRED at 2 mg/kg on day 1, followed by 1 mg/kg on days 2 through 5.

DEX at a dose of 0.6 mg/kg has been studied extensively in patients with croup without serious reported adverse effects.[34-38] The maximum intramuscular dose of DEX used in a previous study was 15 mg.[31] Because we were using 4-mg tablets of DEX, our maximal dose was 16 mg. All doses were rounded to within 15% of the desired dose of 0.6 mg/kg, which enabled the pharmacy to dispense the tablets in 2-mg (½ tablet) increments.

Children in the DEX group did not have longer ED stays or an increase in the rate of hospitalization compared with children in the PRED group, suggesting that both steroids have similar time to onset of action. There was also no significant difference in the persistence of symptoms between groups in the 10 days after ED discharge. Although the study groups were well matched, there was a trend toward a higher rate of inhaled steroid use in the DEX group (19%) versus that in the PRED group (14%; Table I). Inhaled steroid use may be a surrogate marker for disease severity. However, in this study the relative risk of relapse in the children in the DEX group versus that in the children in the PRED group who were taking inhaled steroids was 1.21 (95% CI, 0.38, 3.84); thus there was no apparent effect of inhaled steroid use on the likelihood of relapse in either treatment group.

Because the relapse rate was not different between groups, a 2-dose DEX regimen dispensed from the ED may be preferred because of improved compliance. Many of our patients do not understand the importance of anti-inflammatory therapy. When combined with limited financial resources and inadequate follow-up with their primary care physician, compliance with any oral medication regimen can become a serious problem. Oral DEX is generically available, inexpensive (a 4-mg tablet costs 7 cents in our pharmacy vs 10 cents/mL for Prelone), and well tolerated orally.

This study was not double-blind because DEX tablets were used versus PRED suspension or tablets. Potential investigator bias was limited, because the decision to return for further treatment after discharge from the ED was

made by the parent without investigator input. The use of a third group of patients as an untreated control group would not have been ethical, because corticosteroid therapy has proven value in managing and preventing relapse in acute asthma.

Further studies are required to determine whether a smaller dose of DEX is as effective as the 0.6 mg/kg dose and whether children with mild asthma exacerbations can be treated effectively with 1 dose of DEX given in the ED. The potential role of inhaled corticosteroids in the prevention of relapse is also not clearly defined.

In conclusion, for the management of acute asthma, symptom improvement and the relapse rate were similar between children who received 2 doses of oral DEX or 5 doses of oral PRED. Advantages of DEX include fewer doses, reduced emesis, and a decrease in the number of school/work days missed. Patient compliance may also be improved by dispensing the second dose of medication from the ED. DEX is a practical alternative to PRED in the management of asthma exacerbations in children.

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