Adverse Behavioral Effects of Treatment for Acute Exacerbation of Asthma in Children*

A Comparison of Two Doses of Oral Steroids

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Objective: **To determine the relative adverse symptomatic effects and benefits of therapy with oral corticosteroids at doses of 2 mg/kg vs 1 mg/kg daily in children with acute exacerbations of asthma.**

Methods: **Using a questionnaire that addressed symptoms, we conducted a prospective study of the adverse effects and benefits of therapy with prednisone or prednisolone at two dose levels in 86 children who were 2 to 16 years of age with mild persistent asthma during an acute exacerbation and were unresponsive to therapy with inhaled steroids and β-adrenergic agents. Parents and physicians were blinded to the dose level. Children were assigned to either of the two doses by random allocation. Behavioral side effects were assessed via a questionnaire administered by a physician. Benefits were measured by the resolution of asthma symptoms (cough, shortness of breath, and wheeze) at the completion of the treatment with oral steroids.**

Results: **Behavioral side effects, particularly anxiety ($p < 0.02$) and aggressive behavior ($p < 0.002$), were twice as common in patients receiving a dose of 2 mg/kg/d. Benefits were comparable in the two groups. The number needed to harm (*ie*, the number of patients receiving experimental treatment that would lead to one additional person being harmed vs patients receiving standard treatment) was 6.1 for anxiety, 8.6 for hyperactivity, and 4.8 for aggressive behavior.**

Conclusions: **Because the adverse side effects were greater at the higher dose but the benefits were comparable, we recommend using an oral corticosteroid dose of 1 mg/kg daily for children with mild persistent asthma who present with an acute exacerbation of asthma.**

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Key words: adverse effects; asthma; benefit; prednisolone; prednisone; side effects; therapeutic use

Abbreviations: ARI = absolute risk increase; CI = confidence interval; MDI = metered-dose inhaler; NNH = number needed to harm

Short courses of prednisone, 1 to 2 mg/kg daily for 3 to 10 days, are recommended for the management of acute exacerbations of asthma in children.[1] The recommended steroid dose for acute exacerbation of asthma in adults is 40 to 60 mg oral prednisone daily,[1] which corresponds to < 1 mg/kg daily at an average body weight of 70 kg. We could find no evidence in the literature that 2 mg/kg is more beneficial than 1 mg/kg in treating children. Furthermore, studies in asthmatic children have looked primarily at efficacy and parental management practices, rather than at the possible adverse effects.[2–6] Because the parents of many of our patients have voiced concern about the behavioral changes in their children during short courses of treatment with oral steroids, we decided to conduct a prospective, randomized, blinded trial comparing the adverse effects and the benefits at the two dose levels. We hypothesized that a daily dose of 1 mg/kg would have a lower adverse effect/benefit ratio than 2 mg/kg daily.

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Materials and Methods

The Institutional Review Committee of Bridgeport Hospital approved the study. Patients presenting at the hospital or an outpatient asthma center with persistent asthma were identified. Informed consent was obtained. Patients aged 2 to 18 years were eligible for inclusion if at baseline they had mild persistent

asthma based on National Institutes of Health guidelines (cough, shortness of breath, or wheeze more than twice a week but less than once a day and similar nighttime symptoms more than twice a month but less than once a week), were receiving inhaled steroids (fluticasone, 44 μg [two puffs] bid) daily and were using an albuterol metered-dose inhaler (MDI) as needed. Exclusion criteria were history of chronic lung disease other than asthma; cardiac, liver, or renal disease; attention deficit disorder; previous or current history of psychiatric illness; and use of oral steroids within the previous 2 weeks. Indications for therapy with oral steroids were an incomplete response to therapy for acute symptoms with β-agonists and inhaled steroids. Incomplete response to therapy was defined as persistence of cough, shortness of breath, or wheeze after receiving three β-agonist treatments via nebulizer over a 1-h period or lack of response to three β-agonist treatments of 2 to 4 puffs by MDI over 1 h.[1] Of the 92 families that we contacted, 4 refused to participate. Therefore, 88 children were enrolled in the study.

Sample size was determined assuming an equal allocation ratio between the groups, a type 1 error of 0.05, an excess of risk of 20% assuming a baseline adverse symptom prevalence of 5%, and a desired power of 80%.[7] Patients enrolled in the study were given one of two different doses of oral steroids using a random allocation chart based on a table of random numbers.[8] The randomization code was held by the nursing staff at the asthma center. Group 1 received a 5-day course of prednisone or prednisolone, 1 mg/kg/d bid, and group 2 received a 5-day course of prednisone or prednisolone, 2 mg/kg/d bid, up to a maximum of 60 mg/d prescribed by a resident physician or nurse practitioner. The parents, principal investigator, and primary care physician were not told which dose of oral steroids the child was receiving. Information obtained included age, sex, racial background, and current medications, including the dose, frequency, and method of administration of β-adrenergic agents and inhaled steroids and the presence of any side effects from them. Participants were asked whether systemic symptoms associated with a viral upper respiratory infection, such as headache, nasal congestion, running nose, and fever, were present. At the end of the 5-day course, the parents responded to a questionnaire by the principal investigator (SK) via telephone, mentioning the most common reported side effects of oral steroids (Table 1). The parents were asked specifically whether any of the side-effect symptoms were present before the patient began receiving oral steroids. Responses were considered positive only if the symptoms were absent prior to the initiation of steroid therapy. As anxiety, hyperactivity, and short attention span could also follow the use of β-adrenergic agents, we considered a response to be positive only if the symptom was present for ≥ 4 h after the last dose of albuterol was given. Also, we asked about any associated systemic symptoms. Finally, we asked whether the asthma symptoms (cough, shortness of breath, and wheeze) had resolved at the end of treatment with oral steroids.

Two weeks later, a second telephone contact was made with the parents. We chose 2 weeks because this period would be sufficient for the washout of steroids. Parents were asked whether the patients had used any additional medications since the oral steroid treatment. Benefit was defined as the resolution of asthma symptoms, (cough, shortness of breath, and wheeze) and the absence of relapse. Relapse was defined as the presence or worsening of cough, wheezing, visits to the physician's office or emergency department, or admission to the hospital. The information given by parents was verified by calling the pediatrician and checking hospital admission records. Ascertainment of data from all parents during the study was aided by the fact that the hospital of record for these patients is the only one in the county and the patients are obligated to see their primary care physician.

One month later, the patients with behavioral symptoms were seen for a follow-up appointment while they continued receiving baseline medications except oral steroids.

Table 1—*Common Side Effects Questionnaire

Did you notice any of the following in the past 5 days?
Facial fullness
Facial redness
Changes in appetite
Abdominal pain
Diarrhea
Quiet and reserved manner
Euphoria (excessive happiness)
Depression
Anxiety
Hyperactivity with or without short attention span
Aggressive behavior

*The medical term *euphoria* was explained to the family in simple English as excessive happiness. To check the reliability of the parents' answers, questions were asked about symptoms that are unlikely to be caused by oral steroids: stiff neck, toothache, earache, hematuria, and hemoptysis.

Data Analysis

Side effects and benefits were compared for groups 1 and 2. The analysis was facilitated with a statistical software package (Statistica, version 6; StatSoft, Inc; Tulsa, OK). Differences in mean age were compared using the Student *t* test. Differences in proportions were evaluated using the χ^2 test. Two-tailed p values are presented, and a p value of < 0.05 was considered statistically significant. Risk ratios for the side effects were computed comparing group 2 with group 1, and 95% confidence intervals (CIs) were calculated.[9] The absolute risk increase (ARI) was defined as the absolute difference in rates of adverse events in children receiving the two doses. The number needed to harm (NNH) was defined as the number of patients receiving the experimental treatment that would lead to one additional person being harmed compared with patients who receive the standard treatment. NNH is the reciprocal of the ARI (1/ARI) and was calculated with corresponding 95% CIs.

Results

Of 92 families asked to participate, 88 were enrolled. The age, sex, and ethnic distribution in the two groups were comparable. Patients in both groups received three doses of albuterol, 2.5 mg, in a 1-h period. None of the patients needed to be admitted to the hospital. Oral prednisone or prednisolone was prescribed at the discretion of the physician, plus albuterol MDI, 2 puffs q6h for 5 days. As the maximum dose was 60 mg, one child in group 2 did not receive the 2 mg/kg/d dose. All the patients were given a written action plan.

In the first telephone contact made on day 5 of oral steroid treatment, the parents reported that all the patients in both groups (group 1, 44 patients; group 2, 44 patients) had received the 5-day course of oral steroids and used the albuterol MDI every

Table 2—*Age, Sex, and Ethnic Distribution

Characteristic	Group 1 (n = 43)	Group 2 (n = 43)
Age, yr	7.1 ± 0.6	6.3 ± 0.46
Median	6	6
Range	2–15	2–16
Preschool (age ≤5 yr)	19 (44.1)	18 (41.8)
School age (age ≥6 yr)	24 (55.8)	25 (58.1)
Sex		
Male	30 (69.7)	29 (67.4)
Female	13 (30.2)	14 (32.5)
Race		
White	28 (65.1)	29 (67.4)
African-American	1 (2.3)	3 (6.9)
Hispanic	14 (32.5)	11 (25.5)

*Values given as mean ± SD or No. (%), unless otherwise indicated.

6 h. Compliance with medications was determined by the parents' reports. All patients doubled their dose of inhaled steroids. One patient in group 1 was excluded because the albuterol dosage was increased to every 4 h, and one patient in group 2 was excluded because the inhaled steroid (fluticasone) dose was increased to 110 μg and the albuterol MDI was used every 4 h. Therefore, the study included 86 patients. Thirty-three patients in group 1 and 32 patients in group 2 received oral steroids in suspension, while 10 patients in group 1 and 11 patients in group 2 received oral steroid pills. Table 2 provides the patients' age, sex, and ethnic distribution.

Table 3 illustrates the side effects reported. Anxiety ($p < 0.02$) and aggressive behavior ($p < 0.002$) were statistically more prevalent in group 2. Anxiety, aggressive behavior, and hyperactivity were each reported in nine children, but not the same set of nine children. Hyperactivity was more common ($p = 0.1$) in group 2. This difference might have been statistically significant with a larger sample yielding greater power. All questions that were designed to test the reliability of parents' answers yielded negative responses in both groups.

Table 4 illustrates the estimated ARI and NNH. The NNH values for anxiety, hyperactivity, and aggressive behavior were 6.1, 8.6, and 4.8, respectively. Table 5 shows that there was no statistically significant difference in symptoms between the two age groups of preschool and school-age children. Although the differences in proportions with symptoms suggested that older children were at higher risk for anxiety and hyperactivity, our subgroup sample was too small to make any reliable conclusions.

One month later, the parents were questioned about the persistence of adverse behavioral symptoms. Only one child in group 2 was reported to have persistent anxiety. The others reported no continuing adverse effects. Three patients in group 1 and four patients in group 2 experienced systemic effects (headache, malaise, body aches, changes in appetite, and abdominal pain) prior to receiving therapy with oral steroids and had no change in these symptoms during the treatment. We assumed the symptoms were related to concurrent viral infection. At the end of the 2 weeks, all patients in group 1 and all but one patient in group 2 reported complete resolution of asthma symptoms (cough, shortness of breath, and wheezing). One patient in group 2 needed a second course of oral steroids for worsening of symptoms 2 weeks after the discontinuation of therapy with oral steroids. A review of the hospital admission records and pediatrician records validated this information.

Discussion

While the two dose regimens did not produce different benefits in terms of asthma symptoms, behavioral side effects, particularly aggressive behav-

Table 3—*Side Effects

Symptom	Group 1 (n = 43)	Group 2 (n = 43)	p Value†	Relative Risk Group 2/Group 1 (95% CI)
Facial fullness	6 (13.9)	6 (13.9)	1.0	1.0
Facial erythema	6 (13.9)	7 (16.2)	0.8	1.2 (0.4–3.2)
Changes in appetite	5 (11.6)	5 (11.6)	1.0	1.0
Abdominal pain	2 (4.6)	3 (6.9)	0.7	1.5 (0.3–8.5)
Diarrhea	1 (2.3)	1 (2.3)	1.0	1.0
Anxiety	2 (4.6)	9 (20.9)	0.02	4.5 (1.0–19.6)
Euphoria	2 (4.6)	2 (4.6)	1.0	1.0
Depression	2 (4.6)	0	0.1	0.1 (0–5.4)
Quiet and reserved	2 (4.6)	3 (6.9)	0.6	1.5 (0.3–8.5)
Hyperactive	4 (9.3)	9 (20.9)	0.1	2.25 (0.85–6.7)
Aggressive behavior	0	9 (20.9)	0.002	∞ (1.1–∞)

*Values given as No. (%), unless otherwise indicated.
†Comparison between groups 1 and 2.

Table 4—*ARI and NNH*

Symptom	ARI	95% CI	NNH (1/ARI)	95% CI
Facial fullness	0	−14.6–14.6	∞	−6.8–6.8
Facial erythema	2.3	−12.8–17.4	43.4	−7.8–5.7
Changes in appetite	0	13.5–13.5	∞	−7.4–7.4
Abdominal pain	2.3	−7.5–12.1	43.4	−13.3–8.26
Diarrhea	0	−5.6–5.6	∞	−17.8–17.8
Anxiety	16.3	2.6–30.0	6.1	38.4–3.3
Euphoria	0	−8.8–8.8	∞	−11.3–11.3
Depression	4.6	−1.6–10.8	21.7	−62.5–9.25
Quiet and reserved	2.3	−7.5–12.1	43.4	−13.3–8.2
Hyperactivity	11.6	−3.3–26.4	8.6	−30.3–3.7
Aggressiveness	20.9	8.9–32.9	4.8	11.2–3.0

ior and anxiety, were twice as common in patients receiving the 2 mg/kg daily dose. Parents reported that these behavioral symptoms resolved after the discontinuation of oral steroid therapy.

We considered whether reporting bias by the parents could account for the observed difference in behavior. The parents did not know the study outcome variables when the subjects were enrolled in the study and were not aware that behavioral side effects were an end point. No information was given to the parents at the time of obtaining informed consent or thereafter that could have influenced their response. The telephone follow-ups were performed to ask for all the side effects in a systematic, balanced, and equitable manner, attempting to prevent the appearance of a leading question. The impression conveyed to the parents was that they should report side effects only if they were present above the baseline for their child. It would have been ideal to have the interviewer blinded to the study questions, but every effort was made to avoid any appearance of bias during the telephone interview. The interview was conducted based on a script that encompassed all the side effects that have been reported in the literature as well as associated systemic symptoms. The parents may have had biases based on previous experience with oral steroids, but no such bias was communicated to us before or during the study. The patients enrolled at the hospital and the asthma center were similar based on the enrollment criteria. The incidence of enrollment failure was similar in both places. The management protocol used is the one commonly practiced by most pediatricians.

Table 5—*Symptoms Grouped by Age**

	Group 1		Group 2	
Symptom	Preschool (n = 19)	School (n = 24)	Preschool (n = 18)	School (n = 25)
Anxiety	1 (5.2)	1 (4.1)	3 (16.6)	6 (24)
Hyperactivity	1 (5.2)	3 (12.5)	3 (16.6)	6 (24)
Aggressive behavior			4 (22.2)	5 (20)

*Data expressed as No. (%).

We could find no evidence that the differences in behavioral symptoms could be explained by differences in sex or racial composition between the groups or by the parents' reliability in responding to the questionnaire. Because the dose and frequency of administration of β-adrenergic agents were the same in the two groups and the symptoms persisted beyond 4 h after the use of a β-adrenergic agent, we concluded that the differences in symptoms were not explained by the use of those medications. The precision with which parents noticed the side effects during the 2-h span existing 4 h after the dose of albuterol can be questioned from both an underreporting and an over-reporting standpoint. However, the reliability of parents as historians was supported by their negative replies to side effects not related to oral steroids. There were systemic symptoms that are usually reported with viral upper respiratory infections, a common trigger for acute exacerbations of asthma. It is possible that a drug interaction between the higher dose of steroids and β-adrenergic agents could contribute to the difference in anxiety and aggressiveness. However, no such observation has been reported.

The behavioral symptoms manifested by our patients were similar to those described in adults receiving corticosteroids. Steroid psychosis has been reported in doses as low as 40 mg/d in adults, and psychotic reactions are twice as likely to occur during the first 5 days of treatment vs later.[10] Hyperactivity, aggressive behavior, and severe insomnia also have been described in a 5.5-year-old psychologically stable child within 48 h of receiving 200 μg budesonide by inhalation, with improvements in the child's symptoms after the dose was reduced by half.[11] Another reversible side effect seen in children receiving 2 to 4 mg/kg prednisone daily for 1 week is hepatomegaly. The children were being treated for asthma, nephrotic syndrome, rheumatoid fever, systemic lupus erythematosus, idiopathic thrombocytopenic purpura, Stevens-Johnson syndrome, aplastic anemia, hemolytic anemia, infantile spasms, and giant cavernous hemangioma.[12]

We chose to evaluate the resolution of symptoms based on history rather than measured physiology because management of asthma by pediatricians is based on symptomatic improvement. Although it is possible that physical examination, clinical asthma scoring, or systematic evaluation of pulmonary function testing might have uncovered differences between the two groups, this study was not designed to

test for such differences. We conclude that the evaluation was reliable because the information given by parents was verified by the pediatrician and hospital records. We doubt that significant differences in the degree of improvement between the two groups could have been missed.

The therapeutic benefit of using a dose of 2 mg/kg rather than one of 1 mg/kg has not been documented. In a randomized, double-blind study in children, it was reported that with acute exacerbation of asthma, there was no significant difference in the pattern of recovery in groups of patients receiving prednisolone 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg daily, and therefore it was recommended that doses as low as 0.5 mg/kg be used for short courses in children based on a flat dose-response curve for corticosteroid therapy.[13] Likewise, in a randomized double-blind placebo study, Marquette et al[14] compared doses of 1 and 6 mg/kg methylprednisolone in 23 adults who had been admitted to the hospital for acute exacerbations of asthma and saw similar improvements in lung function in the two groups.

The pediatric dosing of prednisone is generous compared with adult dosing. Nevertheless, a drug may be administered on a higher per-kilogram basis in children based on pharmacokinetic and pharmacodynamic profiles (distribution volume, metabolism, and protein binding). However, our review of the literature revealed that the optimum recommended dose of oral steroids is based not on such considerations, but rather on clinical efficacy. Therefore, the comparison of the two doses is valid so long as the efficacy is comparable and side effects are fewer.

The clinical application of the reported findings should be limited to patients with mild persistent asthma with exacerbations of asthma who are receiving prednisone or prednisolone and do not require admission to the hospital, and our findings cannot necessarily be extended to patients with moderate or severe persistent asthma. However, it is our opinion that there is little reason to believe that patients with more severe asthma may behave differently.

With the increased incidence of asthma now being reported around the world, the short-term use of oral steroids for acute exacerbations has become more prevalent. Therefore, many more children are receiving short courses of oral steroids. We know nothing about the long-term complications of short courses of oral steroids on bone chemistry and growth or on cognitive and emotional development. Because the aim of any treatment is to get the best possible results with the fewest possible side effects, it may be prudent and safer to use the lower dose of 1 mg/kg. Finally, we recommend that a larger cohort of children, including the full range of age, sex, and ethnicity, and with different levels of asthma severity, be included in further investigations of adverse behavioral and biochemical effects of oral corticosteroids.

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