Controlled Trial of Oral Prednisone in the Emergency Department Treatment of Children With Acute Asthma
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Controlled Trial of Oral Prednisone in the Emergency Department Treatment of Children With Acute Asthma

Richard J. Scarfone, MD; Susan M. Fuchs, MD; Alan L. Nager, MD; and Steven A. Shane, MD

ABSTRACT. Background. Recent studies have shown that the use of parenteral corticosteroids in the emergency department decreases the hospitalization rate for patients with acute asthma. We studied the efficacy of oral corticosteroids in the emergency department treatment of moderately ill children with acute asthma.

Methods. Emergency department patients aged 1 through 17 years whose chief complaint was acute asthma were assigned a pulmonary index, based on clinical evaluation. Those with a moderate exacerbation (pulmonary index = 9 through 13) received either 2 mg/kg of oral prednisone or placebo in a randomized, double-blind fashion. Patients in each group were then treated with an identical regimen of frequent aerosolized β2-agonist, for up to a maximum of 4 hours.

Results. Seventy-five patients were assessed. Overall, 11 (31%) of 36 in the prednisone group required hospitalization compared with 19 (49%) of 39 in the placebo group (P = .10). Among the sickest patients (initial pulmonary index > 10), 7 (32%) of 22 prednisone-treated patients required hospitalization compared with 13 (72%) of 18 placebo-treated patients (P < .05). Among patients who had a suboptimal response to initial β2-agonist therapy and who therefore would have been hospitalized had treatment been restricted to 2 hours, 9 (45%) of 20 in the prednisone group ultimately required hospitalization when duration of care was extended 2 additional hours compared with 15 (83%) of 18 in the placebo group (P < .001). In addition, prednisone-treated patients had a significantly greater improvement in median pulmonary index (5.0 vs 3.0, P < .001).

Conclusions. These data demonstrate that oral prednisone, within 4 hours of its administration, reduced the need for hospitalization among a subset of children treated in the emergency department for acute asthma. Pediatrics 1993;92:513-518; acute asthma, oral prednisone, emergency department, β2-agonist, hospitalization.
response to initial $\beta_2$-agonist therapy. A secondary outcome was the degree of improvement in pulmonary index (PI).

METHODS

Patients

The study group included children 1 through 17 years of age with acute asthma treated in the ED of Children's Hospital of Pittsburgh between January 1991 and April 1992. Patients were considered for enrollment if they had had at least one prior episode of wheezing and came to the ED with a moderate exacerbation, as defined by clinical criteria. Exclusion criteria were as follows: the use of inhaled or systemic corticosteroids within the previous 72 hours; concurrent stridor with wheezing; possible foreign body aspiration; history of bronchopulmonary dysplasia, cystic fibrosis, liver or renal disease, congenital heart disease, or sickle cell anemia; or pregnancy. Patients with bronchiolitis, pneumonia, or repeated vomiting were excluded as follows. First, for the months of January 1991 through March 1991 and December 1991 through March 1992, the lower age limit for inclusion was raised to 18 months. Patients between 18 and 24 months who were enrolled during these winter months were subsequently excluded if a nasopharyngeal swab tested positive for the respiratory syncytial virus. Second, the acquisition of chest radiographs was at the discretion of the house officer responsible for overall patient management. If a chest radiograph was obtained and found by a staff radiologist to be consistent with pneumonia, the patient was excluded. Finally, we excluded patients who vomited the study drug within 15 minutes of receiving it and vomited a subsequent dose. The protocol was approved by the hospital's institutional review board.

Protocol

Upon arrival in the ED, eligible patients were examined by a study investigator and assigned an initial pretreatment PI (Table 1). Those with a PI greater than 8 were considered for enrollment; children judged to be having a severe exacerbation (PI > 13) were not enrolled. After informed consent was obtained, all patients were treated with albuterol (2.5 mg in 3 mL of normal saline) by nebulization. Within 5 minutes of completing the first albuterol treatment, patients received either 2 mg/kg of prednisone (Deltasone, Upjohn) or placebo, in a double-blind fashion. This was administered by a nurse not involved in the study; in the absence of the investigator. All doses were rounded off to the nearest 5 mg, with a maximum dose of 60 mg. The identical capsules containing either crushed prednisone tablets or lactose placebo were prepared by the hospital pharmacy. Patients unable to swallow the intact capsules were given the contents mixed with 5 mL of juice. The dose was readministered to any patient who vomited within 15 minutes; those who vomited the subsequent dose within 15 minutes of its administration were excluded. Supplemental oxygen was provided for any patient with an initial oxygen saturation of $\leq 92\%$ in room air, as measured by pulse oximetry.

After being given the initial albuterol treatment and the study drug, all patients received subsequent albuterol treatments following an identical, structured protocol. The first three nebulizations were given at 30-minute intervals and if additional treatments were required, they were given 45 minutes apart. Once enrolled, patients who experienced a clinical deterioration were removed from the protocol, treated more aggressively, and hospitalized. Patients were treated in the ED for a maximum of 4 hours. However, all were examined by the investigator prior to each albuterol treatment and those who were substantially improved prior to the 4-hour limit were discharged to home at that time. It is standard practice in this ED for a decision to be made regarding the disposition of an asthmatic patient after approximately 2 hours of therapy. To stimulate this practice, all study patients remaining in the ED 2 hours after receiving the study drug were assigned a preliminary disposition. A preliminary disposition of "admit" was assigned to those who were not likely to improve substantially with an additional brief period of treatment; thus, these patients would have been hospitalized if duration of therapy had been restricted to 2 hours. Patients who were likely to be sent home with minimal additional care were assigned a preliminary disposition of "home." The purpose of this hypothetical interim assessment was to determine the impact that prednisone therapy had on the subset of patients who had a suboptimal response to initial $\beta_2$-agonist therapy and who would have been hospitalized after 2 hours of ED management.

Patients who required ongoing care continued to be treated up to a maximum of 4 hours, at which time the blinded investigator decided patient disposition. The criteria for admission for both the preliminary disposition and the actual final disposition included an oxygen saturation of $\leq 92\%$ in room air or continued significant retractions or continued poor aeration by auscultation.

At discharge from the ED, all patients, whether sent home or admitted, were assigned a second and final PI. Supplemental oxygen was discontinued for 5 minutes prior to the final oxygen saturation determination in room air. Patients sent home were treated with prednisone, 2 mg/kg per day in two divided doses for 5 days, and either oral or inhaled albuterol three times a day for 7 days. Parents were encouraged to return their child to the ED if worsening respiratory distress developed, and all patients received a follow-up phone call 48 hours after the ED visit.

Statistical Analysis

All patient characteristics and results except PI were analyzed to compare the mean or rate for the prednisone group with that of the placebo group. For nonparametric data (PI), the medians for each group were compared. Chi-square or Fisher's Exact Test was used to compare categorical data; Student's t test was used for continuous data, and the Mann-Whitney U test was used for nonparametric data. Interobserver reliability was assessed using the $\kappa$ statistic. A $P$ value of less than .05 was considered statistically significant.

RESULTS

Initially, 81 patients were enrolled; 6 were subsequently excluded. Five prednisone-treated patients were excluded for vomiting (3), pneumonia (1), and bronchiolitis (1). One placebo-treated patient was excluded because of vomiting. Of the remaining 75 patients, 36 were treated with prednisone and 39 with placebo (Table 2).

At the time of initial examination there were no significant differences between the two groups with respect to age, sex, or race (Table 2). The mean age of the prednisone group was 59 months (range, 12 through 204 months) compared with 63 months.

### TABLE 1. Pulmonary Index

<table>
<thead>
<tr>
<th>Score</th>
<th>Respiratory Rate*</th>
<th>Wheezing†</th>
<th>Inspiratory-Expiratory Ratio</th>
<th>Accessory Muscle Use</th>
<th>Oxygen Saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>$\leq 30$</td>
<td>None</td>
<td>2:1</td>
<td>None</td>
<td>99-100</td>
</tr>
<tr>
<td>1</td>
<td>31-45</td>
<td>End expiration</td>
<td>1:1</td>
<td>+</td>
<td>96-98</td>
</tr>
<tr>
<td>2</td>
<td>46-60</td>
<td>Entire expiration</td>
<td>1:2</td>
<td>++</td>
<td>93-95</td>
</tr>
<tr>
<td>3</td>
<td>$&gt;60$</td>
<td>Inspiration and expiration without stethoscope</td>
<td>1:3</td>
<td>+++</td>
<td>$&lt;93$</td>
</tr>
</tbody>
</table>

* For patients aged 6 or older: through 20, score 0; 21 through 35, score 1; 36 through 50, score 2; $>50$, score 3.
† If no wheezing due to minimal air entry, score 3.
nisone-treated patients would have been hospital-
hours after the study drug was given, 56% of pre-
judging the need for hospitalization been rendered 2
after 2
therefore given a preliminary disposition of "admit"
required hospitalization compared with 72% of placebo-treated patients.

Among prednisone-treated patients, 22 (61%) of 36
required hospitalization compared with 49% of pa-
patients in the placebo group. The median P1 for those treated with
was a significant difference in hospitalization rates and hospitalization rates for those with an
placebo group. The median P1 for those treated with prednisone decreased from 11.0 to 6.0 compared with
15 (83%) were ultimately hospitalized
Hospitalization was prevented for 55% of patients in the prednisone group by treating them for
hours prior to their ED visit, whereas very few had received the-
ophylline.

Patients in each group had equivalent degrees of
illness at entry as reflected by median PI, mean respiratory rate, and mean oxygen saturation at entry.
Among prednisone-treated patients, 22 (61%) of 36
had an initial PI greater than 10 compared with 18
(46%) of 39 in the placebo group (P = .19).

Overall, 31% of patients in the prednisone group required hospitalization compared with 49% of pa-
tients in the placebo group (P = .10, Table 3). There was a significant difference in hospitalization rates for patients with the most severe disease (initial PI > 10). Forty (53%) of the 75 study patients had an initial PI greater than 10. Among this group, 32% of prednisone-treated patients required hospitalization compared with 72% of placebo-treated patients (P < .05).

There was also a significant difference in hospital-
ization rates for patients who had a suboptimal re-
ponse to initial β2-agonist therapy and who were therefore given a preliminary disposition of "admit"
after 2 hours of care (Table 4). Had decisions regarding
the need for hospitalization been rendered 2
after the study drug was given, 56% of pred-
insone-treated patients would have been hospital-
ized compared with 46% of placebo-treated patients (P = .42). However, when treatment was continued
for an additional 2 hours, of the 20 patients in the prednisone group who would have been hospital-
ized after 2 hours, 9 (45%) ultimately required hos-
pitalization. In contrast, of the 18 patients in the pla-
cebo group needing to be hospitalized after 2 hours, 15
(83%) were ultimately hospitalized (P < .05).
Therefore, hospitalization was prevented for 55% of patients in the prednisone group by treating them for
just 2 additional hours.

Prior to the study’s onset, patients were examined
simultaneously by the investigators, who each re-
corded a PI. There was 83% interobserver agreement.
The median final PI was significantly higher for all patients requiring hospitalization compared with all
those discharged to home (8.0 vs 6.0, P < .000001).
Prednisone-treated patients had a significantly
greater decrease in median PI compared with the
placebo group. The median PI for those treated with
prednisone decreased from 11.0 to 6.0 compared with
a decrease from 10.0 to 7.0 for placebo-treated pa-
tients (P < .001).

Three patients (two placebo, one prednisone) ex-
perienced a clinical deterioration soon after study enrollment, necessitating removal from the protocol
and more aggressive treatment. They were not as-
signed a preliminary disposition or a final PI, but
were included in the analysis of overall hospitaliza-
tion rates and hospitalization rates for those with an
initial PI greater than 10.

All 45 patients discharged from the ED were con-
tacted by phone 48 hours after the visit. There was a
0% relapse rate: none of these patients experienced

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**TABLE 2.** Patient Characteristics at Entry

<table>
<thead>
<tr>
<th></th>
<th>Prednisone (n = 36)</th>
<th>Placebo (n = 39)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, mo (SD)</td>
<td>59 (47)</td>
<td>63 (49)</td>
<td>.36</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>26 (72)</td>
<td>28 (71)</td>
<td>.83</td>
</tr>
<tr>
<td>White, No. (%)</td>
<td>19 (53)</td>
<td>17 (44)</td>
<td>.43</td>
</tr>
<tr>
<td>Mean hours of</td>
<td>15 (14)</td>
<td>16 (20)</td>
<td>.36</td>
</tr>
<tr>
<td>wheezing (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline use in previous 24 h, No. (%)</td>
<td>3 (8)</td>
<td>3 (8)</td>
<td>.62</td>
</tr>
<tr>
<td>B2-Agonist use, No. (%)</td>
<td>1 h prior</td>
<td>9 (25)</td>
<td>12 (31)</td>
</tr>
<tr>
<td></td>
<td>24 h prior</td>
<td>24 (67)</td>
<td>.63</td>
</tr>
<tr>
<td>Mean No. of prior admissions (SD)</td>
<td>1.5 (1.8)</td>
<td>1.6 (1.7)</td>
<td>.47</td>
</tr>
<tr>
<td>Initial PI*</td>
<td>11.0</td>
<td>10.0</td>
<td>.13</td>
</tr>
<tr>
<td>Mean respiratory rate (SD)</td>
<td>47 (15)</td>
<td>45 (13)</td>
<td>.22</td>
</tr>
<tr>
<td>Mean O2 saturation (SD)</td>
<td>93.5 (2.9)</td>
<td>94.0 (2.2)</td>
<td>.19</td>
</tr>
</tbody>
</table>

* Pulmonary index; expressed as median.

**TABLE 3.** Hospitalization Rates*

<table>
<thead>
<tr>
<th></th>
<th>Prednisone</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>11/36 (31)</td>
<td>19/39 (49)</td>
<td>.10</td>
</tr>
<tr>
<td>Patients with initial PI &gt; 10</td>
<td>7/22 (32)</td>
<td>13/18 (72)</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

* Values expressed as No. hospitalized/total (%). PI, pulmonary index.

**TABLE 4.** Outcome for Patients With a Preliminary Disposition (PD) of "Admit"*

<table>
<thead>
<tr>
<th></th>
<th>PD of &quot;Admit&quot;</th>
<th>Final Disposition for Those With PD of &quot;Admit&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>20/36 (56)</td>
<td>9/20 (45)</td>
</tr>
<tr>
<td>Placebo</td>
<td>18/39 (46)</td>
<td>15/18 (83)</td>
</tr>
<tr>
<td>P value</td>
<td>.42</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

* Values expressed as No. (%).
clinical worsening necessitating a return visit to the ED or to a private physician.

DISCUSSION

This study demonstrated that oral prednisone was efficacious in reducing the need for hospitalization among a subset of children treated in the ED for acute asthma. This benefit was achieved within 4 hours of prednisone’s administration and was seen among patients treated frequently with β2-agonist aerosols. There have been several recent studies showing corticosteroids to be efficacious in the management of acute asthma, but none demonstrated the efficacy of oral therapy in the ED and none showed a corticosteroid benefit in the setting of frequent β2-agonist therapy. Storr et al16 randomly assigned 140 children hospitalized with acute asthma to receive oral prednisolone or placebo soon after admission. At a median time for reexamination of 5 hours, 30% of patients in the prednisolone group were discharged to home compared with 3% in the placebo group (P < .0001). However, since these patients were relatively undertreated with β2-agonists, a steroid benefit in addition to that achieved with frequent β2-agonist therapy alone was not demonstrated. Tal et al.12 randomly assigned 74 children between 6 and 60 months of age in the ED with acute wheezing to receive either 4 mg/kg of intramuscular methylprednisolone or placebo. After 3 hours, 20% of steroid-treated patients required hospitalization compared with 43% in the control group (P < .05). However, these patients were also relatively undertreated with β2-agonists, perhaps making it possible to discern a steroid benefit. Also, it is feasible that some of the younger infants were wheezing secondary to bronchiolitis and that such patients may respond differently to corticosteroid therapy than do older children with asthma. Littenberg and Gluck13 randomly assigned 97 adults in the ED with acute asthma to receive either 125 mg of intravenous methylprednisolone or placebo. Only 19% of steroid-treated patients required hospitalization, compared with 47% in the control group (P < .003). However, an early clinical benefit after steroid administration was not shown since patients were treated for up to 12 hours in the ED. Also, patients only received β2-agonist aerosols every 2 hours.17 In contrast, Stein and Cole15 treated adults with acute asthma with 125 mg of intravenous methylprednisolone or placebo, followed by frequent β2-agonist aerosols. They found no difference in hospitalization rates between the two groups. However, the failure to detect a steroid benefit was most likely the result of the administration of methylprednisolone to some patients in the placebo group, rather than the use of aggressive β2-agonist therapy.17

A recent meta-analysis of steroid therapy concluded that the oral and intravenous routes are equally efficacious in the initial hours of treatment of acute asthma.18 In fact, Ratto et al.19 found no significant differences in pulmonary function tests 6 hours after steroid dosing among hospitalized adults treated with oral and intravenous steroids. Engel et al20 randomly assigned hospitalized adults to receive either intravenous methylprednisolone or oral prednisone. There were no significant differences between the two groups as assessed by hourly measurements of peak expiratory flow during the first 24 hours after admission.

In a recent review of a 1-year experience at a children’s hospital, it was found that only 4% of 3358 children with acute asthma received systemic steroids in the ED, yet 26% were ill enough to require hospitalization.21 Establishing intravenous access in a child is often labor-intensive, time-consuming, and painful and may be a primary reason for the underutilization of corticosteroids in the ED. The principal benefit of oral prednisone, then, may be that moderately ill patients will receive corticosteroid therapy more consistently and more promptly.

There are several aspects of the present study that deserve further comment. This study did not attempt to find the time needed for prednisone’s peak clinical effect. Recent National Institutes of Health guidelines state that a patient’s ED disposition should be decided 2 hours after steroid administration.22 In our study, a similar percentage of patients in each group would have been hospitalized had therapy been restricted to 2 hours. However, more than half of those prednisone-treated patients who would have been hospitalized after 2 hours were able to be discharged to home within the next 2 hours; yet hospitalization was prevented in only 17% in the placebo group. Both groups continued to be treated with frequent β2-agonists after the 2-hour preliminary disposition was rendered. Presumably, then, the lower hospitalization rate for prednisone-treated patients reflected the onset of action of prednisone after the initial delay known to occur with corticosteroid therapy.23-25 It is possible that with a longer period of treatment the prednisone group would have had an even lower hospitalization rate. However, 4 hours was considered to be a reasonable duration to treat sick asthmatic patients within the constraints of most busy EDs.

It was decided to stop the study earlier than originally planned when, after an interim review by the study investigators, it was found that three of four study outcomes achieved statistical significance in favor of the use of prednisone. Based on our data and that of others,12-14,16 it seemed unethical to fail to treat moderately ill asthmatic patients with corticosteroids, even though this represented the standard of care at this and other centers at the time.18 As a result of stopping the study prematurely, the overall hospitalization rate between the two groups did not achieve statistical significance (P = .10). This failure to achieve statistical significance reflects the observation that many patients experienced a prompt clinical benefit from β2-agonist aerosols only and were able to be sent home without the need for corticosteroid therapy. When we considered only those patients with an initial suboptimal response to β2-agonist therapy, there was a significantly lower hospitalization rate for the prednisone group. Since it is not possible to preselect those patients who will respond
promptly to $\beta_2$-agonists, we would advocate treating all moderately ill asthmatic children with prednisone.

The PI is a clinical asthma score that has been shown to correlate significantly with objective pulmonary function studies and hospitalization rates in children older than the age of 6 treated for acute asthma. Subsequently, it has been used in the assessment of younger children. Since our patient population had a wide age range, we modified this PI by adding a second respiratory rate scale. Also, since others have shown that oxygen saturation correlates with clinical scores, pulmonary function tests, and the need for hospitalization in children with acute asthma, we included oxygen saturation as an additional piece of objective data. It was felt that the modified index, while closely approximating which has been validated, would better serve as a tool to identify moderately ill children in our patient population. In fact, it was found that patients requiring hospitalization had a significantly higher median PI than those who were able to be sent home. Also, there was 83% interobserver agreement among the four study investigators assigning PI scores to patients ($\chi$ statistic).

There was some overlap among patients with an initial PI greater than 10 and those given a preliminary disposition of "admit." However, although there were 24 patients who met both of these criteria, an additional 30 patients met one, but not both, of these criteria.

The need for hospitalization was based on the physical examination conducted by the blinded investigators. Guidelines used for admission decisions included an oxygen requirement, continued significant retraction, or continued poor aeration. More explicit criteria for admission were purposely avoided in order to simulate the decision-making as it is carried out in most EDs: that is, reliance on clinical judgment. Also, the lack of explicit admission criteria would better serve as a tool to identify moderately ill children in our patient population. In fact, it was found that patients requiring hospitalization had a significantly higher median PI than those who were able to be sent home. Also, there was 83% interobserver agreement among the four study investigators assigning PI scores to patients ($\chi$ statistic).

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REFERENCES


GENETIC SCREENING AND THE INSURANCE INDUSTRY

What would happen if the insurance company was unaware of important unfavorable information that was known to the applicants? In these instances, serious errors in risk classification would occur. Certain individuals would receive their insurance at unreasonably low cost. More claims would be filed than were expected, and, if a significant number of these risk classification errors were made, the financial status of the entire insurance pool would be adversely affected...

Attending physicians will probably begin to use new diagnostic tests that can identify genetic diseases and diseases with a genetic predisposition shortly after the tests are developed. As mentioned above, insurers have no current interest in ordering such tests themselves. Nonetheless, although they may prefer to avoid ordering genetic tests, it could be extremely important that insurers have access to prior test results. Why? If this information were unavailable to the insurer at the time of underwriting, then applicants who already knew, through tests performed by their attending physicians, that they were likely to experience early death or illness could buy large amounts of insurance coverage at prices that failed to reflect this increased risk. In the aggregate, this practice could involve disproportionately large numbers of applicants and/or highly significant amounts of insurance. The ensuing claims would markedly exceed projected losses, and everyone within the insurance pool would suffer.


Submitted by Morris A. Wessel, MD
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