Association Between Reported Use of Inhaled Triamcinolone and Differential Short-term Responses to Aerosolized Albuterol in Asthmatics in an Emergency Department Setting*

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Forty-four adult patients with acute asthma were treated with albuterol at a rate of 15 mg/h over 2 h. Analysis of covariance showed a significantly higher baseline adjusted mean for both percent predicted forced expiratory volume in 1 s (PFEV1) (p=0.045) and percent predicted forced vital capacity (PFVC) (p=0.022) at 50 and 110 min for the patients who reported triamcinolone use. Although heart rates decreased overall during the first hour of albuterol treatment, a rise in mean heart rate occurred during the second hour of treatment only in patients reporting triamcinolone use (p=0.05). After accounting for the effects of parenteral corticosteroids, the effect of reported triamcinolone use remained significant. These data suggest that use of inhaled corticosteroids in this context may be associated with enhanced local and systemic β-responsiveness, and if a causal relationship could be confirmed, this may constitute yet another advantage of early inhaled corticosteroid treatment in asthma. These data also suggest that chronotropic effects of high-dose albuterol should be monitored in patients using inhaled triamcinolone.

(Chest 1994; 106:452-57)

**Key words**: adult; β-agonist; corticosteroid; high dose

Recent approaches in asthma therapy have focused on treating the inflammatory aspects of the disease.1,2 The role of corticosteroids especially has been re-examined. Present recommendations have included use of inhaled corticosteroids even in patients with mild asthma as well as early use of systemic corticosteroids in patients suffering from acute asthma in the emergency department.3 Although the anti-inflammatory effects of corticosteroids are well described, some reports have also suggested that these agents may also enhance β-agonist responses.3,4

The manner in which β-agonists are used in acute asthma has also changed. Reports have been published describing high-dose albuterol or terbutaline, administered both by intermittent as well as continuous aerosolization to children and adults with acute asthma.5-8 Present recommendations call for albuterol administration at a much higher frequency in patients with acute asthma seen in the emergency department than that normally used in ambulatory patients.9 The authors have been examining the efficacy and safety of high-dose albuterol in adults with acute asthma in an emergency department setting.10 In the present study, reported corticosteroid administration was related to albuterol responses in patients with acute asthma in an attempt to examine the assertion that β-responsiveness is affected by corticosteroid administration. A significantly different pattern of response was observed in patients who claimed to be taking aerosolized triamcinolone. The characteristics of the patients with respect to corticosteroid administration, spirometric response, and changes in heart rate are thus detailed in this report.

**Materials and Methods**

Between August 1991 and April 1992, 38 adult asthma patients were entered into an institutional review board-approved emergency department study10 that randomized subjects into albuterol aerosol treatment at a rate of 15 mg/h over 2 h by either continuous or intermittent modes. The former was delivered over 50 min each hour by large reservoir nebulizer (HEART system, Vortran Medical Technology, Sacramento, Calif) while the latter was delivered 5 mg every 20 min by acorn-type jet nebulizer (Weeneb Marquest Medical Products, Englewood, Colo). The key entry criteria for these patients was that in addition to having asthma,11 at the time of presentation, a hand-held peak expiratory flow meter reading was less than 300 L/min for men and 250 L/min for women.

Parenteral methylprednisolone (125-mg bolus) was administered at the discretion of the study physicians at the end of 1 h of therapy. Aminophylline was not administered to study patients. Details of this study are described elsewhere.10 These data were analyzed and did not show a significant difference in overall spirometric responses between the modes of nebulization, but
they did suggest a possible benefit for patients who had an initial percent predicted forced expiratory volume in 1 s (FEV1) of less than 50 percent. Thus, it was decided to study patients in this category.

Six more such adult asthmatics were treated in January 1993 (also randomizing the mode of nebulization) before the study was terminated. The 44 patients were pooled for analysis in this study. The same questionnaire was administered to all the subjects and included questions about concurrent disease, prior hospitalizations and emergency visits, current and past outpatient medications, demographic information, cigarette smoking, duration of asthma, atopic family history, and home/occupational environments.

Spirometric measurements consisted of forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) and were made at times 0, 50, and 110 min using a dry rolling-seal spirometer (Ohio Medical Supply, Houston). The FVC and percent predicted FVC (PFVC) were calculated using the Kory/Polgar reference values12 with no corrections for ethnicity. Vital signs, the presence of tremor or agitation, and symptoms of side effects were also determined at these time points. Peak flow measurements were not recorded.

A computer program (SAS PROC GLM or LOGISTIC programs, SAS Institute, Cary, NC) was used for all multiple variable analyses. Differences between groups (two tailed) were compared using Student's t test for continuous variables and Fisher's exact test for categoric variables. Logistic regression was used to analyze proportional differences in heart rate increases from time 50 min to time 110 min after adjusting for other variables. A significant effect was defined by a p value of less than or equal to 0.05. Not significant (NS) is defined as p>0.05. Means are reported with standard deviations for all tables, and with standard errors for all figures. Analysis of variance for repeated measures13 with baseline adjustment (analysis of covariance, [ANCOVA]) was used to analyze between-group differences in dependent variables at 50 and 110 min. The main dependent variables were PFEV1, PFVC, and heart rate. The main independent variables were the reported history of triamcinolone use. A secondary independent variable examined was the administration of parenteral corticosteroids. Baseline measurements were highly correlated (p≤0.001) with the subsequent values at 50 and 110 min and showed significant (p≤0.001) covariate effects in all respective ANCOVA. There was homogeneity of regression for covariates across effect groupings with respect to dependent variables.

**RESULTS**

Of the 44 patients studied, 23 received albuterol by intermittent aerosol treatment while 21 had continuous albuterol aerosolization. Thirteen of the 44 patients reported using inhaled corticosteroid and the only preparation used was triamcinolone. None of these patients were receiving oral corticosteroids. Of the 31 other patients, 3 were receiving oral prednisone at the time of examination, 2 at 10 mg/d and 1 at 50 mg/d. Some of the baseline characteristics of the study patients are listed in Table 1. Of six patients who received intravenous corticosteroids at 1 h, three were in the triamcinolone group. Of three patients who were admitted to the hospital, two were in the triamcinolone group.

The mean age of the study patients was 40.9±12.9 years, with a predominance of Hispanic patients (58 percent) followed by African-Americans (40 percent), with the remainder being whites. Fifty-five percent of patients had Medicaid or Medicare/SSI. There was no significant difference in age, ethnicity, or payment mode between patients who claimed triamcinolone use and those who did not. No patients had observable tremor at study entry but 11 had tremor at the end of the study treatment period. Three of these 11 patients claimed to be using inhaled triamcinolone.

There was no difference in heart rate, PFEV1, or PFVC response between those who received continuous compared with those who received intermittent albuterol aerosol (ANCOVA, p>0.5 for all analyses). Subsequent analysis models, therefore, examined the impact of corticosteroids on spirometric and heart rate values without including nebulization mode since the latter contributed little to the variance of dependent variables.

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**Table 1—Baseline Characteristics of Study Subjects**

<table>
<thead>
<tr>
<th>Continuous nebulization</th>
<th>Patients Reporting No Triamcinolone Use, n=31 (%)</th>
<th>Patients Reporting Triamcinolone Use, n=13 (%)</th>
<th>Significance of Difference Between TR and non-TR Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of rhinitis</td>
<td>45.2</td>
<td>53.9</td>
<td>NS</td>
</tr>
<tr>
<td>History of smoking</td>
<td>74.2</td>
<td>38.5</td>
<td>0.040</td>
</tr>
<tr>
<td>Receiving β-agonists</td>
<td>35.5</td>
<td>15.4</td>
<td>NS</td>
</tr>
<tr>
<td>Receiving cromolyn</td>
<td>87.1</td>
<td>100</td>
<td>NS</td>
</tr>
<tr>
<td>Receiving methylinthines</td>
<td>9.7</td>
<td>7.7</td>
<td>NS</td>
</tr>
<tr>
<td>Receiving oral steroids in past month</td>
<td>74.2</td>
<td>100</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>54.8</td>
<td>53.9</td>
<td>NS</td>
</tr>
<tr>
<td>Relatives with atopic disease</td>
<td>61.3</td>
<td>61.6</td>
<td>NS</td>
</tr>
<tr>
<td>Mean duration of asthma, yr</td>
<td>20.4±13</td>
<td>22.6±16.6</td>
<td>NS</td>
</tr>
<tr>
<td>Median emergency visits in past year</td>
<td>6</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline PFEV1</td>
<td>43.9±19.9</td>
<td>48.9±14.5</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline PFVC</td>
<td>58.9±15.5</td>
<td>66.5±10.1</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline heart rate</td>
<td>92.3±15.4</td>
<td>97.7±18.2</td>
<td>NS</td>
</tr>
<tr>
<td>Age, yr</td>
<td>38.7±13.7</td>
<td>46.2±9.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Categoric variables expressed as the percentage of the group with that characteristic. NS=not significant. TR=triamcinolone.
The overall PFEV₁ at 50 min and 110 min was higher for patients reporting triamcinolone use (ANCOVA, p=0.045) compared with those who did not. The responses are shown in Figure 1. The overall PFVC at 50 min and 110 min was higher for patients reporting triamcinolone use (ANCOVA, p=0.022). The PFVC responses for the two groups are shown in Figure 1. Heart rates showed a difference in the rate of change between 50 and 110 min (Fig 2) between those who did and did not report triamcinolone use (ANCOVA, p=0.005). Patients reporting triamcinolone use had a significantly higher proportion of individuals with heart rate increases from time 50 min to time 110 min (p=0.005). Adjustments for whether patients showed heart rate increases between baseline and 50 min or whether patients showed baseline heart rates greater than 100/min did not change this significant association. The proportion of individuals with heart rate increases from baseline to 50 min was not significantly different for patients reporting triamcinolone use.

Age did not show a significant covariate effect on
heart rates, PFEV₁, or PFVC (data not shown). Diastolic and systolic blood pressure as well as FEV₁/FVC ratios did not show any significant changes with time, nebulization mode, or inhaled triamcinolone grouping (data not shown). A history of smoking did not show any effect on heart rates, PFEV₁, or PFVC (data not shown).

Because parenteral corticosteroids were given in six patients at 1 h, the effect of this additional treatment was explored by assessing the time-related effect of this intervention using two-way ANCOVA with triamcinolone usage and parenteral steroid administration as independent variables on 50- and 110-min values, with baseline values as the covariate. There was a significant time by parenteral steroid effect (p=0.044) on PFEV₁ as well as on PFVC (p=0.001). Graphic depiction of these effects is illustrated in Figure 3. There was a higher slope of the mean spirometric values at times 50 to 110 min in those who received parenteral corticosteroids. Including the parenteral steroid effects did not diminish the significance of reported triamcinolone use effect for either PFEV₁ (p=0.038) or PFVC (p=0.017). With heart rate as the dependent variable, no overall slope difference was associated with parenteral steroids (p=0.214), but there was still a significantly higher slope between 50 min and 110 min for patients reporting triamcinolone use (ANCOVA, p=0.001). Graphic depiction of this is shown in Figure 2.

**DISCUSSION**

These data demonstrate a significant association between reported triamcinolone use and altered responses to albuterol aerosol at a fixed dose. Other studies have examined the role of corticosteroids in enhancing β₂-agonist responses. In the Dutch nonspecific lung disease study, inhaled corticosteroids enhanced responses to β₂-agonists overall in ambulatory asthmatics. Ellul-Micallef and Fenech demonstrated an enhanced FEV₁ response to isoproterenol (Isopenrolone) in 10 patients with stable asthma treated with one intravenous 40-mg dose of prednisolone compared with placebo. Klaustermeyer and Hale also reported improvement in bronchospasm after 125 mg of methylprednisolone. To our knowledge, however, an enhanced response in patients with acute asthma has not been demonstrated. Littenberg and Gluck demonstrated an admission rate benefit in asthmatics in the emergency department treated with a single initial bolus of methylprednisolone but did not systematically follow airflow measurements at set intervals. The hospital discharge PFEV₁ was somewhat (p=0.068) higher for patients treated with methylprednisolone in that study. The data in our study support a possible role for inhaled corticosteroids in enhancing responses to albuterol with respect to PFEV₁ as well as PFVC.

Presently used inhaled corticosteroid preparations are used in preference to oral corticosteroids because they have a higher anti-inflammatory profile and less systemic effects. Nevertheless, systemic effects have been reported in asthmatic patients treated with routine doses. For example, a slowing of growth in children treated with budesonide, a potent topical corticosteroid in use in Europe, has been reported.

![Graph](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21698/ on 04/28/2017)
Budesonide inhalations can affect osteocalcin levels.\textsuperscript{17} Some effects of inhaled corticosteroids on the adrenal axis have also been reported.\textsuperscript{18,19} The possibility that systemic absorption may lead to enhanced \( \beta \)-responsiveness in the cardiovascular system is supported by the finding in the present study of an increase in heart rates between the first and second hours of albuterol treatment. This effect was of a greater significance level than that observed for spirometric responses. Taylor et al.\textsuperscript{20} reported that normal subjects had biochemical but not cardiovascular response differences to \( \beta \)-agonists when treated with prednisone, 30 mg/d, for 1 week compared with placebo. The amount of albuterol used, however, was only 10 mg compared with the 30 mg used in our study. The heart rate pattern observed in the present study suggests that initial heart rate reflects heightened sympathetic stimulation from acute asthma that subsides quickly after 50 min of albuterol treatment-induced bronchodilation. Subsequently, however, the continued presence of albuterol and perhaps its serum accumulation appear to cause heart rate increases at 110 min only in the patients reporting triamcinolone use. That this is due to a subtle upregulation of \( \beta \)-responsiveness by triamcinolone is a hypothesis that requires further study. Another possible related explanation for the observed heart rate increases in the triamcinolone group is that systemic corticosteroid absorption may have reversed the cardiovascular tolerance to \( \beta \)-agonists.\textsuperscript{21}

The present study did not verify triamcinolone or albuterol serum levels nor did it examine regularity of medication use. Also, the study was not one designed to experimentally test the effects of triamcinolone, so that the apparent effects seen may not have been causally related to triamcinolone alone. Furthermore, the role and magnitude of recent oral corticosteroid administration could not be accurately assessed. Selection bias may have resulted in the more severely ill asthmatics receiving triamcinolone inhalation from their providers. This may relate to \( \beta \)-agonist tachyphylaxis\textsuperscript{22} and, therefore, to decreased bronchodilatory response to albuterol treatment. The patients treated with triamcinolone, however, showed the opposite; namely, an enhanced bronchodilatory response with time. This suggests that this type of selection bias cannot explain the observed response patterns. However, since the frequency and dose of \( \beta \)-agonist use was not determined in this study, accurate deductions about tachyphylaxis likelihood cannot be made. A difference in cardiovascular \( \beta \)-responsiveness may be especially important in the context of the trend toward using higher doses and more frequent administrations of \( \beta \)-agonists in treating asthma. Cardiovascular toxicity may be associated with high-dose albuterol treatment in adults.\textsuperscript{5}

This study suggests a possible enhanced \( \beta \)-responsive state associated with inhaled corticosteroid use in asthmatics. If it could be confirmed that corticosteroids can enhance bronchodilatory responses in patients with acute asthma, it would have implications in the treatment of status asthmaticus. If intravenous corticosteroids improve overall short-term bronchodilation induced by short-term \( \beta \)-agonist administration, it may be better to administer intravenous corticosteroids initially in severe cases even without waiting for initial \( \beta \)-agonist treatment response, a course presently recommended by the National Institutes of Health expert panel.\textsuperscript{9} Although the number of patients treated was too small to accurately assess effect, a possible beneficial effect of intravenous corticosteroid treatment was observed for both PFEV\textsubscript{1} and PFVC in the short time frame of the present study, suggesting a rapid positive treatment effect on both airway obstruction as well as on air trapping and dynamic compression of this treatment in acute asthma.\textsuperscript{23} On the other hand, if intravenous corticosteroids only improve short-term \( \beta \)-agonist responses in those who have not been using inhaled (and/or oral) corticosteroids, a more selective approach to giving initial steroids may be more appropriate. The apparent bronchodilator-enhancing effect of inhaled corticosteroids, if confirmed, would constitute another advantage for using this medication in maintenance treatment for patients with frequent exacerbations not controlled with as-necessary \( \beta \)-agonist therapy. The possible effect on cardiovascular \( \beta \)-responsiveness also suggests that chronotropic effects of high-dose albuterol should be monitored in patients who have been using inhaled triamcinolone, especially with prolonged albuterol treatment.

ACKNOWLEDGMENTS: The authors are grateful to Stephen Briggs III of B&B Technology and to Vortran Medical Technology, for providing the Vortran HEART nebulizers.

REFERENCES

8 Lin RY, Smith A, Hergenroeder F. High serum albuterol levels and tachycardia in adult asthmatics treated with high-dose continuously aerosolized albuterol. Chest 1993; 103:221-25
11 American Thoracic Society. Standards for the care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987; 136:225-44