A Randomized Controlled Trial of Methylprednisolone in the Emergency Treatment of Acute Exacerbations of COPD*

Charles L. Emerman, M.D.; Alfred F. Connors, M.D.; Thomas W Lukens, M.D.; Michael E. May, M.D.; and David Effron, M.D.

We conducted a randomized, controlled double-blind study to determine whether intravenous administration of methylprednisolone early in the therapy for acute exacerbations of COPD would improve pulmonary function in the Emergency Department and reduce the need for hospitalization. Ninety-six patients completed the study. All were at least 50 years of age and had no history of asthma. Patients received aminophylline and hourly administration of aerosolized isethionate. Methylprednisolone (100 mg) or physiologic saline solution was given within one-half hour of arrival in the Emergency Department. Spirometry was performed initially and after the third and fifth aerosol treatments. We found no greater improvement in FEV₁ in the group receiving the steroid (37 percent) than in the control group (43 percent; NS). There was also no difference in the rate of hospitalization (33 percent in the steroid-treated group vs 30 percent in the control group; NS). We conclude that early administration of methylprednisolone does not affect the emergency phase of treatment for acute exacerbations of COPD. *(Chest 1989; 95:563-67)*

The use of steroids in patients with COPD is controversial. Some studies have demonstrated a response to prednisolone in patients with stable COPD, while other investigators have found a response only in selected subpopulations.¹ The design and the conclusions of these studies have been criticized by several reviews and studies which have found no benefit to steroid administration;²⁻⁴ however, there is evidence to suggest that steroids are effective in the treatment of episodes of acute exacerbation of COPD.⁵ In a randomized controlled trial of repeated parenteral doses of methylprednisolone, Albert and colleagues⁷ demonstrated a significant improvement in pulmonary function after 12 hours of therapy in patients hospitalized with acute exacerbations of COPD.

Corticosteroids have an established role in the emergency treatment of acute asthma. Previous studies have shown an improvement in clinical status and pulmonary function for asthmatic patients treated with these agents.⁸⁻¹⁰ Recent evidence indicates that early use of corticosteroids in the Emergency Department can result in a lower rate of hospitalization for patients with acute asthma;¹¹⁻¹³ however, there has not been previous investigation to determine whether similar rapid improvement would occur in patients with acute exacerbations of COPD.

The purpose of this study was to further investigate the use of steroids in the acute exacerbation of COPD by determining whether the early use of methylprednisolone in the Emergency Department could improve pulmonary function and minimize the need for hospitalization of these patients.

**Materials and Methods**

**Population**

Patients with a clinical history of emphysema or chronic bronchitis¹⁵ presenting to the Emergency Department with acute respiratory distress were considered for entry into the study. The criteria for inclusion in the study were established before the trial and were strictly observed. All patients were at least 50 years of age and had initial spirometry in the Emergency Department with an FEV₁ less than 70 percent of predicted or a FEV₁/FVC% less than 60 percent. Patients were excluded from the study if they had a history of asthma,¹⁶ onset of episodes of respiratory distress before the age of 35 years, or if they had received oral or intravenous steroids within one month of presentation. Patients were also excluded if found to have pneumonia, acute congestive heart failure, or other conditions mandating admission to the hospital. All patients gave informed written consent to a protocol approved by the hospital's human investigation committee.

**Therapy**

After informed consent had been obtained, blood was drawn for a complete blood cell count, determination of theophylline level, and arterial blood gas analysis. A portable anteroposterior chest roentgenogram was obtained in all patients. After initial testing was done, therapy was initiated with hourly administration by hand-held nebulizer of 0.5 ml of 1 percent isethionate diluted 1:4 with physiologic saline solution, continuous oxygen by nasal cannula,
and an intravenous infusion of aminophylline at a dose of 0.6 mg/kg/h. After the serum level of theophylline was determined, patients were given a loading dose of aminophylline calculated to raise their theophylline level to 10 μg/ml to 20 μg/ml. No antibiotics were given during the period of study.

Patients were randomly assigned to receive either methylprednisolone (100 mg) or an equivalent volume of placebo solution within one-half hour of arrival in the Emergency Department. The vials were prepared by the hospital pharmacy in a predetermined random order and were identical in appearance and labeling. The patients, treating physicians, and investigators remained blinded to the contents of the vials until the termination of the study.

Following five hourly aerosol treatments, therapy was terminated, and the patients were either admitted or discharged according to the judgment of the treating physician, with no further therapy. Patients could be discharged earlier if they were free of wheezing and were no longer dyspneic. Patients who were discharged were asked to return to the Emergency Department 48 hours later for reevaluation and repeat spirometry. Patients were considered to have suffered a relapse if they required an unscheduled return visit to the Emergency Department within 48 hours of discharge. Patients who did not return as scheduled were contacted by telephone. Patients for whom follow-up information or baseline spirometry was not available were excluded from the final analysis of data.

**Measurements**

Spirometry was obtained in the Emergency Department using a computerized, portable, Fleisch pneumotachographic type of spirometer (Spiroscan 1000). The spirometer was calibrated at least every 48 hours with a 3-L, calibrated syringe. The spirometer was always accurate within 30 ml (1 percent) of the calibrating volume. Spirometry was obtained with the patient seated and wearing nose clips. Two or more forced expiratory curves meeting accepted standards were obtained. The curve with the best FVC was used. Spirometry was obtained at the initiation of therapy and after the third and fifth aerosol treatments. Baseline spirometry was obtained during a period of clinical stability in all patients in our clinical pulmonary function laboratory either before, or one month after, entry into the study.

**Analysis**

Categoric data were evaluated using the χ² test with Yates' correction for continuity. Continuous variables, including the spirometric data, were analyzed using Student's t-test. A value of p < 0.05 was taken to indicate statistical significance. All data are reported as the mean ± SEM.

**RESULTS**

This study was conducted from October 1986 until November 1987 in the Emergency Department of Cleveland Metropolitan General Hospital, a large urban county institution. One hundred patients were initially entered into the study. Four patients were lost to follow-up and did not have follow-up spirometry. The remaining 96 patients consisted of 50 men and 46 women with an average age of 64.0 ± 0.8 years. Ninety-five percent of the patients had a history of chronic bronchitis, while 64 percent of the patients had a history of emphysema. Eighty-four percent (81) of the patients were using theophylline products, while 75 percent (72) of the patients had received a β-adrenergic-agonist inhaler. Ninety-one percent (87) of the patients had a present or past history of smoking cigarettes. There were 44 patients in the control group, with 52 patients in the steroid-treated group. There was no difference between the two groups in age, medication use, cigarette smoking, or duration of illness. The initial theophylline level, WBC, and arterial blood gas levels were similar in the two groups. The baseline spirometric data from pulmonary function tests performed during a period of clinical stability were similar for the two groups. These data are summarized in Table 1.

On arrival in the Emergency Department, the initial FEV₁ was 26 ± 2 percent of predicted normal value in the control group, while it was 29 ± 2 percent of the predicted normal value in the steroid-treated group (NS). The initial FVC was 38 ± 3 percent of predicted normal in the control group and 38 ± 2 percent of predicted normal in the steroid group (NS). The patients in the control group were treated for an average of 4.4 ± 0.1 hours (range, 2.5 to 6 hours), while those in the steroid-treated group were treated for 4.5 ± 0.1 hours (range, 3 to 7 hours; NS).

After treatment the FEV₁ was 35 ± 2 percent of predicted normal in the control group and 38 ± 2 percent of predicted normal in the steroid-treated group (NS). The FVC was 47 ± 3 percent of predicted normal in the control group and 50 ± 2 percent of predicted normal in the steroid-treated group (NS). The percentage of improvement in the FEV₁ and FVC was the same in the two groups (Fig 1). There was no difference in the proportion of patients in each group who required admission to the hospital (Table 2). There was also no difference between the groups in

<table>
<thead>
<tr>
<th>Data</th>
<th>Steroid-Treated Group</th>
<th>Control Group</th>
</tr>
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<tbody>
<tr>
<td>No. of subjects</td>
<td>52</td>
<td>44</td>
</tr>
<tr>
<td>Age, yr</td>
<td>63.7 ± 1.2</td>
<td>64.3 ± 1.3</td>
</tr>
<tr>
<td>Cigarette use, pack-years</td>
<td>56.5 ± 4.9</td>
<td>62.4 ± 5.0</td>
</tr>
<tr>
<td>Theophylline level, μg/ml</td>
<td>9.6 ± 1.0</td>
<td>9.2 ± 1.0</td>
</tr>
<tr>
<td>WBC × 10³</td>
<td>9.1 ± 0.4</td>
<td>9.5 ± 0.5</td>
</tr>
<tr>
<td>Po₂, mm Hg</td>
<td>66.0 ± 1.8</td>
<td>64.8 ± 2.5</td>
</tr>
<tr>
<td>Paco₂, mm Hg</td>
<td>38.1 ± 1.0</td>
<td>41.7 ± 1.4</td>
</tr>
<tr>
<td>pH</td>
<td>7.44 ± 0.01</td>
<td>7.43 ± 0.01</td>
</tr>
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*All comparisons between two groups were not significant. Po₂, oxygen pressure; and Paco₂, carbon dioxide tension.
†Performed either prior to or one month after study.

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the proportion of patients who suffered a relapse and required unscheduled visits to the Emergency Department within 48 hours of discharge (10 percent [four] in control group vs 15 percent [eight] in steroid-treated group; NS).

Twenty-eight percent (27) of the patients had an eosinophil count greater than 500 cells/cu mm. Patients with an eosinophil count greater than 500 cells/cu mm did not have a lower rate of hospitalization or a greater improvement in pulmonary function when treated with steroids. Twenty-five percent (24) of the patients had greater than a 15 percent increase in FEV₁ in response to inhaled isoproterenol on baseline pulmonary function testing. In these patients, there was no difference in improvement in FVC or FEV₁ between the control and steroid-treated groups. There was no significant correlation between the percent response to inhaled isoproterenol and the percentage of improvement in FEV₁ in either the steroid-treated group or the studied group as a whole.

Table 2—Results of Treatment*

<table>
<thead>
<tr>
<th>Data</th>
<th>Steroid-Treated Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final FVC, percent predicted</td>
<td>50 ± 2</td>
<td>47 ± 3</td>
</tr>
<tr>
<td>Final FEV₁, percent predicted</td>
<td>38 ± 2</td>
<td>35 ± 2</td>
</tr>
<tr>
<td>Percent change in FEV₁</td>
<td>37 ± 6</td>
<td>43 ± 10</td>
</tr>
<tr>
<td>Hospitalization rate, percent</td>
<td>33</td>
<td>30</td>
</tr>
</tbody>
</table>

*All comparisons between two groups were not significant.

To determine whether patients with more severe COPD responded differently to steroid therapy, we also analyzed a subgroup of patients whose baseline spirometry revealed a postbronchodilator FEV₁ which was less than 60 percent of predicted normal or 60 percent less than a simultaneously obtained FVC. For this analysis, we also eliminated any patient with a 30 percent or greater increase in FEV₁ in response to inhaled isoproterenol. Sixty-six (69 percent) of the patients met these criteria for chronic airflow limitation, with 29 patients in the control group and 37 patients in the steroid-treated group. The average age in this group as 64.7 ± 1.1 years, with 35 men and 31 women. In this subpopulation, there was again no difference in theophylline levels, WBC, arterial blood gas levels, or baseline spirometry between the control or steroid-treated group. The initial FEV₁ was 23 ± 2 percent of predicted normal in the control group and 27 ± 2 percent of predicted normal in the steroid-treated group (NS). The initial FVC was 38 ± 4 percent of predicted normal in the control group and 37 ± 2 percent of predicted normal in the steroid-treated group (NS). In this subpopulation with chronic airflow limitation, there was no difference in FEV₁ after treatment (33 ± 3 percent of predicted normal in control group vs 35 ± 3 percent of predicted normal in steroid-treated group; NS). There was also no difference in FVC after treatment between the control group (48 ± 4 percent of predicted normal) and the steroid-treated group (50 ± 3 percent of predicted normal; NS). The change in FEV₁ with treatment was 48 percent in the control group and 30 percent in the steroid-treated group (NS). Twenty-eight percent (eight) of the control group was admitted, while 35 percent (14) of the steroid-treated group was admitted (NS).

**Discussion**

This randomized, double-blind, placebo controlled study of patients with acute exacerbations of COPD failed to show any decrease in the rate of hospitalization in patients treated with methylprednisolone early in the course of their therapy in the Emergency Department. We found no greater improvement in spirometric values in the treated group than found in the control group. Furthermore, we were unable to identify a subpopulation in which the steroids were beneficial.

Several previous studies that have looked at the effect of steroids in patients with stable COPD have found subpopulations whose condition responds to steroids. In some studies, these subpopulations have included up to 55 percent of the total studied group. In a double-blind crossover study of 24 patients with chronic bronchitis, Shim et al found that seven out of 24 patients showed greater than a 30 percent improvement in FEV₁ with treatment, with 30 mg of
Methylandisole daily. These investigators found that in this subgroup of apparent steroid responders, the majority had a significant response to inhaled bronchodilators and were also characterized by eosinophilia of the sputum. They did not find a correlation with an elevated blood eosinophil count. In another study, Harding and Freedman found that six out of 36 patients appeared to have a response to steroids. The responders were characterized by a high incidence of blood eosinophilia and increased variability in baseline spirometry. These investigators did not find a correlation with sputum eosinophilia or with a response to inhaled bronchodilators. Studies by both Mendella et al and by Blair and Lite found improved FEV in patients treated with steroids. These investigators found that the responders were characterized by an increased responsiveness to inhaled bronchodilators but did not find a correlation with either blood or sputum eosinophilia. Many of these studies have been criticized recently, with questions raised about the size of the studied groups and the representativeness of the studied patients. Eliasson et al found no improvement in pulmonary function in 16 patients treated with prednisolone in a crossover study. We were not able to identify a subgroup of our population that responded to steroids.

Most of the studies on the effectiveness of steroids in patients with COPD have been performed on stable patients. There have been few studies which have examined the effect of steroids in patients with acute respiratory insufficiency. Albert et al studied 44 patients admitted to their hospital with chronic bronchitis, chronic airflow obstruction, and acute respiratory insufficiency with hypoxemia or acute hypercapnia. Patients in their study were randomized to receive either placebo or methylprednisolone (0.5 mg/kg of body weight every six hours). Albert et al found that with the first measurement at 12 hours, the steroid-treated group had a greater improvement in FEV, after bronchodilator and that by 24 hours, there was a significant improvement in FEV, both before and after bronchodilator, which persisted up to the end of the studied period at 72 hours. These investigators were not able to distinguish the steroid responders on the basis of the response to bronchodilators, eosinophil counts, or sputum eosinophilia. The criteria for entry into their study was somewhat stricter than in ours, requiring an FEV, less than 60 percent of normal or an FEV,/FVC% less than 60 percent on baseline testing; however, even when our population is redefined using these criteria, we did not find a significant improvement with steroid treatment. In addition, the study by Albert et al was performed on hospitalized patients over a period of several days, while our study focused on the effect of early administration of steroids on the course and outcome of the patient's visit to the Emergency Department.

There have not been uniform standard criteria for the diagnosis of COPD used in previous studies of steroid effectiveness. Some of these studies have used clinical criteria with evidence of chronic airflow limitation on baseline spirometric testing. Others have excluded patients with responses to inhaled bronchodilators greater than 15 to 30 percent. There is some recent evidence to suggest that the response to bronchodilators is not a reliable method of distinguishing patients with asthma from those with COPD. In our study, there was no difference in the response to steroids in patients with and without a significant (greater than 15 percent) response to bronchodilators on baseline testing.

The relatively short time of treatment in our study may be a factor in the lack of effectiveness of steroids in this population. Our patients were monitored in the Emergency Department for a period of time ranging from 2½ to 7 hours. None of the patients admitted were treated for less than 4½ hours; however, studies of the effectiveness of steroids in acute asthma have found that the onset of the effectiveness occurs relatively quickly. Littenberg and Gluck studied 97 patients with acute asthma in the Emergency Department for an average of four hours and found that 47 percent of the control group required admission, as compared to only 19 percent of the steroid-treated group. There was a trend toward a higher FVC and FEV, in the steroid-treated patients, although this did not achieve statistical significance. Storr et al investigated children admitted to the hospital for status asthmaticus and treated with either oral prednisolone or placebo. These investigators found that within six hours, they were able to discharge 30 percent of the patients in the prednisolone-treated group but only 3 percent of patients in the placebo-treated group. There was also a greater improvement in peak expiratory flow rate in the placebo-treated group. Ellul-Micallef and Fenech found significant increases in peak expiratory flow rate within two hours of oral administration of prednisolone in patients with chronic stable asthma. We did not observe improvement in response to steroids in a 4½-hour period of observation. Although we did not continue spirometric measurements or control treatment after patients were admitted, none of the patients was discharged within 24 hours of their admission to the Emergency Department. Similarly, steroid therapy did not reduce the rate of relapse in patients who were discharged from the Emergency Department; however, the results of the study by Albert et al suggest that patients with acute exacerbations of COPD may require a longer period of time to respond to steroids than do patients with acute asthma.

Our study was limited to the effects of methylpredi-
nisolone on the outcome of therapy in the Emergency Department for an acute exacerbation of COPD. We did not address the effects of short-term treatment with oral steroids on the improvement in pulmonary function of patients following discharge from the Emergency Department, neither did we study the effect of repeated doses of steroids in patients hospitalized for acute exacerbations of COPD. While there is evidence to support the routine use of steroids in acute asthma, our study does not support their routine use in the initial therapy of acute exacerbations of COPD. Further investigation would aid in delineating the circumstances under which steroids are beneficial to patients with acute exacerbation of COPD.

REFERENCES
15 Official statements of the American Thoracic Society: standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987; 135:225-43
17 Ferris BG. Recommended standardized procedures for pulmonary function testing. Am Rev Respir Dis 1978; 118(suppl 1):55-88
22 Ellul-Micallef R, Fenech FF. Intravenous prednisolone in chronic bronchial asthma. Thorax 1975; 30:312-15