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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]

A Randomized Comparison of 100-mg vs 500-mg Dose of Methylprednisolone in the Treatment of Acute Asthma*

Charles L. Emerman, MD; and Rita K. Cydulka, MD

There have been conflicting reports comparing the effects of various doses of corticosteroids in the treatment of acute asthma. The purpose of this study was to compare 100 mg with 500 mg of methylprednisolone in the emergency department treatment of acute asthma. We studied 150 patients presenting to the emergency department with acute asthma. After baseline pulmonary function testing, patients were treated with oxygen and hourly administration of aerosolized albuterol. Patients were randomized to receive either 100 or 500 mg of methylprednisolone intravenously. Spirometry was repeated at 3 h, and again at 5 h for those patients whose dyspnea had not resolved after 3 h. There was no difference in the FEV₁ between the 500-mg and 100-mg dose groups either before treatment (38.0% vs 32.6% of predicted normal) or after treatment (55.3% vs 51.9% of predicted normal). There was no difference in the per-

centage improvement in FEV₁ with treatment between the 500-mg and 100-mg dose groups (65.0% vs 71.2%). Twenty-five percent of the patients in the 500-mg dose group were admitted to the hospital compared with 28% of patients in the 100-mg dose group (not significant). We conclude that the administration of a 500-mg dose of methylprednisolone offers no advantages over a 100-mg dose in the emergency department treatment of acute asthma. (CHEST 1995; 107:1559-63)

NS=not significant

Key words: acute asthma; asthma treatment; β -agonists; corticosteroids

Several studies have shown the effectiveness of the early use of corticosteroids in the emergency department treatment of acute asthma.^{1,2} These studies have found that the early use of corticosteroids leads to a marked decrease in hospitalization rate despite a lack of marked effect on pulmonary function. Although not all the studies have confirmed the effectiveness of corticosteroids,^{3,4} a recent meta-analysis concluded that the early use of corticosteroids reduced hospital admission rates in adults with an odds ratio of 0.47.⁵

The appropriate dose of corticosteroids for use in the treatment of asthma has been unclear. Recent studies of the effects of corticosteroids in the emergency department treatment of asthma have used a variety of doses of methylprednisolone ranging from 125 mg up to 1,000 mg. Some studies have been performed comparing different dosages or different corticosteroid agents in the treatment of acute asthma. Haskell et al⁶ assigned patients to treatment with 15,

40, or 125 mg of methylprednisolone every 6 h for 3 days. They showed that administration of the higher doses led to an earlier and more marked improvement in FEV₁. However, Tanaka et al⁷ compared patients receiving either 20 mg or 125 mg of methylprednisolone and found no difference in improvement of pulmonary function. A meta-analysis of the available studies comparing different doses of corticosteroids has suggested that there may be a benefit to higher doses of corticosteroids.⁵ There has been some suggestion that very high doses of methylprednisolone, up to 1 g/d, may be beneficial in the treatment of severe acute asthma.⁸ This is in contrast to the usual recommendations for administration of 80 to 125 mg of methylprednisolone.⁹

Little of this work assessing the effects of different doses of corticosteroids in the early treatment of acute asthma has been performed in the emergency department. McFadden et al⁴ found no difference in patients treated with 250, 500, or 1,000 mg of hydrocortisone. This study, however, included only 38 patients divided into four treatment groups. Aside from that study, most of the other work has been performed either on outpatients or on patients admitted to the hospital. The purpose of this study was to compare the effects of 500-mg doses of methylprednisolone with 100-mg doses in the emergency department treatment of acute asthma.

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Table 1—Comparison of Baseline Data

	100-mg Dose	500-mg Dose	p Value
Number	74	76	
Gender, F/M	45/29	51/25	NS
Age, yr	35.0 ± 11.9	34.4 ± 11.4	NS
Cigarette use, current/prior/never	23/11/40	25/8/42	NS
Sputum production, %	55	58	NS
History of fever, %	11	8	NS
Outpatient β -agonists, %	85	80	NS
Outpatient theophylline, %	43	47	NS
Inhaled corticosteroids, %	24	16	NS
Prednisone, %	12	7	NS
Pretreatment FEV ₁ , % of predicted normal	33.6 ± 15.1	38.0 ± 17.7	NS

METHODS

This study was performed in the emergency department of MetroHealth Medical Center, Cleveland, a large, urban, county-owned, university-affiliated, hospital. Adult patients presenting with an acute exacerbation of asthma were eligible for enrollment in the study. Patients with a known history of asthma were included if they presented with wheezing, dyspnea, or both along with an FEV₁ that was below 75% of the predicted normal value. Patients were excluded if they had a history of COPD, lung cancer, previous pneumonectomy, brittle diabetes as manifested by hospitalization within the prior 2 months for control of diabetes, or a history of gastrointestinal bleeding within the prior 2 months. Prisoners and pregnant women were excluded, along with patients with clinical evidence of pneumonia, pneumothorax, or decompensated congestive heart failure.

On initial presentation, patients were questioned about medication use, cigarette use, and evidence of infection. Blood was drawn for a complete blood cell count and theophylline level. Spirometry was performed using a computerized, portable, pneumotachograph-type spirometer (Fleisch, SpiroScan 1000, Portland, Ore). Spirometry was performed with the patient seated and wearing noseclips. Three forced vital capacities were obtained with the highest FEV₁ used for analysis. The spirometer was calibrated at least three times a week using a 3-L syringe. Chest radiographs and arterial blood gas values were obtained only at the discretion of the treating physician. Therapy was initiated with oxygen, 3 L by nasal cannula, and nebulized albuterol by air-driven nebulizer. During the course of the study, patients received no other medications, including intravenous aminophylline.

After informed consent had been obtained, patients received, in a randomized, blinded fashion, methylprednisolone, either 100 mg or 500 mg intravenously. The study drug was prepared, at the time of the patient's enrollment in the study, by the hospital pharmacy, using a randomized coding scheme. The investigators, patients, and treating clinicians were all blinded to the dose of the drug being administered. Spirometry was repeated after 3 h. Patients who were clinically free of wheezing and dyspnea could be discharged from the department after 3 h with prescription for inhaled β -agonists and prednisone. Patients who continued to manifest wheezing or dyspnea remained in the department for a total of 5 h. After 5 h, all patients were either admitted to the hospital or discharged from the emergency department. Patients who were discharged from the department were contacted at 2 and 7 days to determine whether they had suffered a relapse, as manifested by a nonscheduled visit to a physician for their asthma.

The χ^2 test was used to analyze differences in categorical vari-

CHANGE IN FEV1 WITH TREATMENT

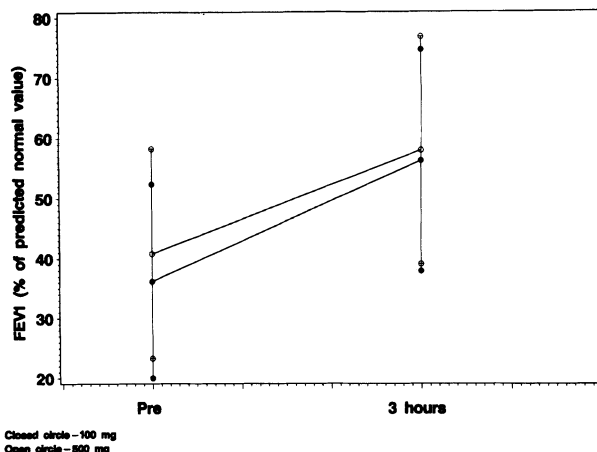


FIGURE 1. Change in FEV₁ with treatment in patients treated for 3 h only. Closed circles=100-mg dose group; Open circles=500-mg dose group; error bars are ± standard deviation.

ables between the two groups. The Student's *t* test was used to assess differences in continuous variables. Repeated measures analysis of variance was used to evaluate changes in pulmonary function in those patients who had spirometry at 3 and 5 h. A *p* value <0.05 was taken to indicate statistical significance. Data are recorded as the mean ± standard deviation. Unless otherwise noted, the FEV₁ is expressed as the percent of predicted normal value. This study was approved by the Hospital's Human Investigation Committee.

RESULTS

This study was performed between February 1992 and August 1993. One hundred fifty patients were enrolled in the study, including 96 women and 54 men with an average age of 34.7 ± 11.6 years. There were 48 current and 19 past cigarette smokers with an average of 22.3 ± 18.6 pack-years of cigarette use. Sixty-nine (46%) patients were using theophylline products; 123 (82.6%) of the patients were using β -agonist inhalers; 10 (6.7%) patients were using ip-

CHANGE IN FEV1 WITH TREATMENT

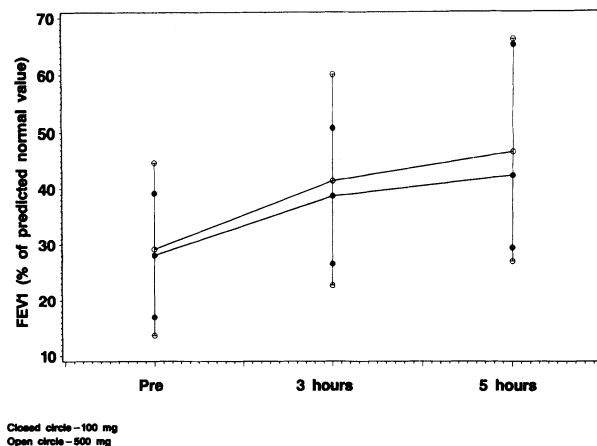


FIGURE 2. Change in FEV₁ with treatment in patients treated for 5 h. Closed circles=100-mg dose group; open circles=500-mg dose group; error bars are ± standard deviation.

Table 2—Results

	100-mg Dose	500-mg Dose	p Value
Hospital admissions, %	28 (21/74)	25 (19/76)	NS
Relapse at 2 days, %	5 (2/42)	11 (4/37)	NS
Relapse at 7 days, %	8 (3/38)	19 (7/37)	NS

ratropium bromide (Atrovent) inhalers; 30 (20%) of patients were using steroid inhalers; and 14 (9.3%) of patients were taking oral prednisone on an outpatient basis. Fourteen (9.3%) of the patients had a history of fever, while 13 (8.9%) of the patients had a history of purulent sputum production. The WBC count averaged $8,860 \pm 302$ cells per cubic millimeter. The theophylline level was 6.6 ± 6.4 $\mu\text{g/mL}$ in patients reporting theophylline use. There was no difference in these variables between the patients receiving a 500-mg dose as compared with those receiving a 100-mg dose of corticosteroids (Table 1).

The pretreatment FEV₁ was $35.9 \pm 16.6\%$ of predicted normal. There was no difference in pretreatment pulmonary function between the 500-mg dose ($38.0 \pm 17.7\%$) and the 100-mg dose group ($33.6 \pm 15.1\%$; not significant [NS]). Posttreatment FEV₁ was $55.3 \pm 19.6\%$ in the 500-mg dose group and $51.9 \pm 18.0\%$ in the 100-mg dose group. The percentage change in FEV₁ with treatment was $65.0 \pm 67.2\%$ in the 500-mg dose group and $71.2 \pm 64.9\%$ in the 100-mg dose group (NS).

One hundred nine patients were discharged from the emergency department after 3 h of treatment. The pretreatment FEV₁ in these patients was $40.8 \pm 17.5\%$ predicted in the 500-mg dose group and $36.2 \pm 16.2\%$ in the 100-mg dose group (NS). After 3 h, the FEV₁ had increased to $58.0 \pm 18.9\%$ in the 500-mg dose and $56.3 \pm 18.4\%$ in the 100-mg dose group (NS). There was a $57.8 \pm 57.0\%$ increase treatment in the 500-mg dose group and $74.0 \pm 68.4\%$ increase in the 100-mg dose group (NS; Fig 1).

Forty-one patients remained for 5 h of therapy. The pretreatment FEV₁ was $29.2 \pm 15.5\%$ in the 500-mg dose group and $28.1 \pm 11.1\%$ in the 100-mg dose group (NS). After treatment, this had increased to $46.6 \pm 19.6\%$ in the 500-mg dose group and $42.3 \pm 12.9\%$ in the 100-mg dose group ($p=0.41$). The percentage increase in FEV₁ pretreatment to posttreatment was 88 ± 90.7 in the 500-mg dose group vs $65.0 \pm 57.6\%$ in the 100-mg dose group ($p=0.36$; Fig 2).

Forty-seven (31.3%) of the patients had severe obstruction on presentation with an FEV₁ less than 25% of predicted normal. The posttreatment FEV₁ in the subset of patients was $37.8 \pm 14.9\%$ in the 500-mg group vs $41.5 \pm 14.3\%$ in the 100-mg group (NS). The percentage improvement pretreatment to posttreatment was $124.8 \pm 82.9\%$ in the 500-mg group vs

$118.0 \pm 72.2\%$ in the 100-mg group (NS).

Twenty-five percent of the patients in the 500-mg dose group were admitted to the hospital as compared with 28% of the patients in the 100-mg dose group (NS; Table 2). We were able to contact 80% of the patients at 2 days postdischarge and 75% of the patients at 7 days postdischarge. Eight percent of the patients had suffered relapse at 48 h, with no significant difference between the groups. Thirteen percent of patients had suffered relapse within 7 days, again with no significant difference between the two groups (Table 2).

We analyzed the data in the subgroup of patients who were already receiving corticosteroids on an outpatient basis, either by inhaler or oral prednisone. There was again no difference in improvement of pulmonary function between the 500-mg and 100-mg dose groups. There was no difference in the hospitalization rate between the two groups.

DISCUSSION

A number of investigators have compared differing doses of corticosteroids in the treatment of asthma. Haskell et al⁶ studied 25 hospitalized patients treated with 15, 40, or 125 mg of methylprednisolone. They found that the conditions of patients in the 125-mg dose group improved significantly by the first day while the conditions of those in the 40-mg and 20-mg dose groups did not improve until the second and third days, respectively. Overall, the improvement in FEV₁ of the 125-mg and 40-mg dose group exceeded that of the 15-mg dose group after 1½ days of treatment. Webb¹⁰ studied the response to 0.2, 0.4, or 0.6 mg/kg of oral prednisolone for 2 weeks after an acute exacerbation. The peak expiratory flow rate was greatest for those patients given the 0.6 mg/kg dose of prednisolone.¹⁰ Britton et al,¹¹ however, found no difference in improvement in peak flow over the course of 8 days among three groups given varying doses of hydrocortisone or methylprednisolone. Harfi et al¹² assessed 21 children admitted to the hospital and treated with either 30 mg/m² of methylprednisolone every 6 h or 300 mg/m² every 6 h. Although the patients in the 300 mg/m² dose group had a somewhat higher posttreatment peak expiratory flow rate, those differences did not reach statistical significance.¹² Pedersen et al⁸ compared six asthmatic patients treated with either 1,000 mg of methylprednisolone daily for 3 days followed by placebo tablets or 50 mg of methylprednisolone intravenously for 3 days followed by tapering doses of oral methylprednisolone and found no differences in pulmonary function between the two groups. Gordon et al¹³ evaluated the effects of two doses of methylprednisolone, 125 mg or 60 mg, against hydrocortisone, 100 mg, on serum IgE levels.

The patients treated with the highest dose of methylprednisolone had a significant fall in IgE levels, while those patients treated either with hydrocortisone or with the lower dose of methylprednisolone did not show such a marked decrease in IgE levels.¹³

Other investigators have also found that there is no difference between varying doses of corticosteroids. Bowler et al¹⁴ studied the response to hydrocortisone given in doses of 50, 100, 500 mg every 6 for 2 days and followed by 20, 40, or 60 mg of prednisone for 12 days, respectively. There was no difference in peak expiratory flow, FEV₁, or dyspnea scores among the groups.¹⁴ Morell et al¹⁵ compared patients given either 2 mg/kg or 10 mg/kg of methylprednisolone against placebo and found no difference in pulmonary function over a 2-day course of treatment. Pierson et al¹⁶ did not show a difference in pulmonary function in children given hydrocortisone, 7 mg/kg, dexamethasone, 0.3 mg/kg/24 h, or betamethasone, 0.3 mg/kg/24 h. Sue et al¹⁷ evaluated 14 patients treated with hydrocortisone, methylprednisolone, or dexamethasone in equivalent dosages. There was again no difference among the three drugs with the exception of transient advantages to hydrocortisone and dexamethasone over methylprednisolone at 12 and 18 h.¹⁷ Raimondi et al¹⁸ studied 40 patients treated as inpatients with hydrocortisone, either 80 mg/kg/d or 6 mg/kg/d. Over the course of 5 days, they failed to find any difference in pulmonary function between the two dosages.¹⁸ McFadden et al⁴ compared the effects of 250, 500, and 1,000 mg of hydrocortisone against placebo in 38 patients treated in the emergency department. There were no differences among any of the three dosage groups, although there was also no difference between the steroid groups and the placebo group.⁴ Finally, one other study has not found any benefit to intravenous corticosteroids in patients hospitalized with severe asthma.¹⁹

To our knowledge, we have reported the largest series to date evaluating the effects of different doses of corticosteroids in the emergency department. This study would have been able to detect an absolute increase in posttreatment FEV₁ (as percent of predicted normal) for the 500-mg group of 7% with a power of 77%. While we saw no difference in response among patients who remained in the study for 5 h, most patients were discharged from the emergency department after 3 h. The size of our study population allowed us to determine that there was no significant difference in the percentage improvement in FEV₁ among patients treated for 5 h with a power of 24%. It is possible that some effect of higher-dose corticosteroids may have been seen had we monitored the patients for a longer period. Ellul-Micallef and Fenech²⁰ found that significant

improvements in pulmonary function were seen within 1 h after intravenous injection of prednisolone, although the peak effect was not seen until 7 to 8 h. Storr et al²¹ found significant improvement in pulmonary function within 5 h after administration of prednisolone to children. In another study, Ellul-Micallef²² administered oral prednisolone and intravenous hydrocortisone to patients with chronic stable asthma. Again, significant improvement from intravenous hydrocortisone was seen within 1 h with a peak effect at 5 h.²² Nevertheless, the results of this study, with the limitations noted above, pertain only to the effects of higher-dose corticosteroids over short-term treatment in the emergency department. Further, this study addresses only the issue of whether there is an advantage to 500-mg doses of methylprednisolone over 100-mg doses. As discussed in the introduction, there are several studies that have not found any benefit to corticosteroid administration in the emergency department. This study does not address that controversy, only the question of the dose if corticosteroids are to be used.

We conclude that 500-mg doses of methylprednisolone offer no advantage to 100-mg doses in the emergency department treatment of acute asthma. The higher dose does not appear to lead to a decrease in hospitalization or a greater improvement in pulmonary function. The current recommendations for the administration of 80 to 125 mg of methylprednisolone appear to be adequate.

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