Controlled trial of intravenous corticosteroids in severe acute asthma

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Abstract

Background The value of corticosteroids in severe acute asthma continues to be debated.

Methods Ninety consecutive patients admitted to the emergency room with severe acute asthma were studied in a randomised, double blind, controlled trial to determine the efficacy of corticosteroids. Eighty two patients completed the study. All received oxygen therapy and intensive bronchodilator treatment. The patients were divided into three groups for steroid treatment, receiving intravenous methylprednisolone 10 mg/kg every four hours for 48 hours (29 patients, group A); intravenous methylprednisolone 2 mg/kg every 4 hours for 48 hours (27 patients, group B); or no intravenous corticosteroids (26 patients, group C).

Results There were no differences on admission among the three groups in forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF), or arterial oxygen or carbon dioxide tension; and the rates of recovery in FEV_1, FVC, and PEF were similar.

Conclusions Corticosteroids given with bronchodilators have not shown a beneficial effect in the first 48 hours of recovery of severe acute asthma. Only in those patients who failed to respond by the third hour of treatment, and in those who were previously taking oral corticosteroids, does a favourable, though not statistically significant, effect appear to occur.

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Administration of corticosteroids both by inhalation and by mouth is widely used in chronic asthma,[1] and oral prednisolone is generally regarded as an effective measure for the control of acute exacerbations.[2]

In severe acute asthma intravenous corticosteroids can achieve a very high plasma concentration and are considered essential treatment for most cases.[3] Until recently, however, the use of corticosteroids was controversial as some studies had shown no differences in the results of treatment with and without corticosteroids.[4 5] On the other hand, Fanta *et al*[6] reported that the administration of corticosteroids over 24 hours in a group of patients with severe acute asthma who did not respond to standard bronchodilator treatment led to a

significantly faster improvement than that seen in those who did not have corticosteroids. Furthermore, a randomised study of patients with severe acute asthma showed that corticosteroids given with bronchodilators significantly reduced the rate of hospital admissions.[7] Others have questioned the efficacy of corticosteroid treatment in all patients with severe acute asthma, although some patients clearly may benefit.[8] No guidelines, however, have yet been established to identify a priori those patients who may benefit from corticosteroids and those who will not, nor has the optimal dose been established.[9–13] We attempted a randomised, double blind, controlled trial to evaluate treatment with intravenous corticosteroid in addition to standard bronchodilator treatment in patients with severe acute asthma.

Methods

Ninety patients with severe acute asthma (as defined by the American Thoracic Society),[14] who had been admitted to the emergency service of a general hospital in Barcelona, were studied for 48 hours. Eighty two patients completed the trial. Eight were excluded owing to incomplete data. All patients received oxygen by Ventimask (fractional inspired oxygen (FIO_2) 0·28) and intensive bronchodilator treatment was administered as follows: adrenaline hydrochloride—three doses of 0·3 mg subcutaneously, one every 15 minutes; aminophylline—5·6 mg/kg in a 20 minute intravenous infusion followed by 0·9 mg/kg/h for 48 hours (as recommended by Mitenko and Ogilvie[15]); inhaled hexoprenaline—5 mg every four hours via a Bird Mark 8 ventilator.

A double blind randomised design was used for the corticosteroid trial, which divided the patients into three groups over the first 48 hours after admission. Thus 29 patients (group A) were given intravenous methylprednisolone (Upjohn) in a dose of 10 mg/kg every four hours for 48 hours; 27 patients (group B) received 2 mg/kg every four hours for the same period; and 26 patients (group C) received as a placebo 2 ml of 0·9% sodium chloride intravenously every four hours for 48 hours. Very high doses of corticosteroids were given to avoid the criticism of inadequate dosage if no beneficial effect were seen. Patients having a maintenance dose of oral corticosteroids (n = 23) continued to receive this treatment throughout the study. Pregnant women and patients with a history of cardiac disease, diabetes, active peptic ulcer, and hypertension with diastolic blood pressure greater than 120 mm Hg were excluded.

Pretreatment data on the three groups of patients with severe acute asthma

Group:	A	B	C
n:	29	27	26
Mean (SD) age (y)	47 (16)	43 (17)	49 (13)
Sex (M/F)	10/19	10/17	10/16
Mean (SD) duration of asthma (y)	11·76 (9·96)	15·72 (12·63)	9·20 (5·92)
Atopic subjects (n)	15	11	16
Mean duration of attack before admission (h)	6·14	8·57	5·95
Previous treatment with β_2 agonists (n)	19	18	15
Regular treatment with oral steroids (n)	11	5	7
Increase in steroid dose before admission (n)	3	3	4
Previous treatment with xanthines (n)	15	17	20
Mean (SD) respiratory values			
FEV$_1$ (l)	0·57 (0·43)	0·71 (0·37)	0·55 (0·22)
FVC (l)	1·05 (0·58)	1·42 (0·63)	1·20 (0·41)
PEF (l/min)	143 (107)	170 (85)	155 (80)
Mean (SD) blood gas tensions (mm Hg)			
Pao$_2$	62·21 (12·11)	63·73 (12·4)	62·65 (11·3)
Paco$_2$	38·07 (7·94)	36·44 (9·45)	37·57 (8·57)
Mean (SD) heart rate/min	108·8 (16·03)	103·9 (13·63)	108·6 (19·8)
Mean (SD) respiration rate/min	28·8 (5·4)	28·4 (6·63)	27·04 (7·57)

FEV$_1$—forced expiratory volume in one second; FVC—forced vital capacity; PEF—peak expiratory flow; Pao$_2$—arterial oxygen tension; Paco$_2$—arterial carbon dioxide tension. Conversion to SI units: 1 mm Hg $\approx$ 0·133 kPa.

The protocol was approved by the hospital scientific committee and informed consent was obtained from each patient before entry to the study. Respiratory rate, heart rate, blood pressure, chest radiograph, electrocardiogram, arterial blood gases during the breathing of room air, and a complete blood count were recorded when they entered. Spirometric measurements of forced expiratory volume in one second (FEV$_1$) forced vital capacity (FVC), and peak expiratory flow (PEF) were also recorded.

The patients were all treated in the emergency room. Spirometry was repeated every hour for the first six hours, and arterial blood gases were measured at the end of the sixth hour. All tests were then repeated at 24 and 48 hours. The FEV$_1$, FVC, and PEF were recorded as absolute values at BTPS, a dry spirometer (Vicatest, Mijnhardt) being used with the patient in a sitting position.

A subgroup analysis was also carried out on those patients receiving regular treatment with oral corticosteroids before admission, those who presented with eosinophil counts above 3·5 × 10^5/l, and those who did not increase their PEF by 15% after three hours of treatment.

STATISTICAL ANALYSIS
Comparability of the pretreatment measurements was tested with the χ^2 test in the case of qualitative variables. For comparison of the means of quantitative variables analysis of variance, with previous verification of the conditions of application (Kolmogoroff-Smirnoff and Bartlett-Box), was performed. The Kruskal-Wallis test was used in cases where these conditions were not met.

For studying the effect of treatment on the different respiratory indices factorial analysis of variance of repeated measurements with constant covariant was carried out, with the pretreatment measurement introduced as covariant.

Results
Patients' data on entry to the study are shown in the table. The three groups were similar in all the variables measured. In particular, there were no significant differences in mean FEV$_1$, FVC, PEF, Pao$_2$, Paco$_2$, heart rate, or respiratory rate among the three groups when the subjects entered the study.

In all three treatment groups there was a gradual increase in FEV$_1$, FVC, and PEF during the 48 hours of the study (fig 1), but there were no significant differences between the rates of increase for the three groups. No significant differences were observed during the study in the changes in Pao$_2$ and Paco$_2$.

There was a significant increase in FEV$_1$ with time (p < 0·005), which was not affected by treatment group. There was also a significant 46·3% increase in PEF with time (p < 0·01), but the increase in FVC by 48 hours was not significantly greater than before treatment (fig 1).

Among patients whose PEF had improved less than 15% above baseline after three hours (nine in group A, 11 in group B, and 12 in group C) there was a trend towards a faster recovery after three hours in patients from group A (fig 2A), but this did not reach statistical significance.

In patients receiving regular treatment with oral corticosteroids before admission (11 patients in group A, five in group B, and seven in group C) an increase in PEF was observed after the third hour of treatment in patients of group A, but this was not significantly different from the subgroups in groups B and C (fig 2B).

No effect on any of the respiratory indices was related to the presence or absence of blood eosinophilia at the time of entry to the study. Six patients complained of epigastric discomfort: two in group A, three in group B, and one in group C. One patient in group B developed melaena from an active duodenal ulcer confirmed by endoscopy. One patient in group B developed transient sinus tachycardia immediately after the first intravenous bolus of methylprednisolone, but this did not occur after subsequent injections.

Discussion
Until a few years ago intravenous hydrocortisone was empirically considered essential for the treatment of severe acute asthma[16 17]; but this view has been questioned in recent papers, which have stated that corticosteroids are of little or no value, even when administered in high doses.[5] Fanta et al,[6] however, found significant differences in the response to treatment over 24 hours in patients with severe acute asthma between those who were given intravenous hydrocortisone and those who were not. The study included only patients who had not responded to treatment with bronchodilators during the previous eight hours. Other recent studies in adults[12] and in children[18] also appear to confirm the beneficial effect of steroids in severe acute asthma.

In a study of 91 admissions for severe acute

Figure 1 Hourly recordings of forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), peak expiratory flow (PEF), and arterial oxygen and carbon dioxide tensions (Pao₂, Paco₂) in the three groups studied. 1 mm Hg ≈ 0·133 kPa.
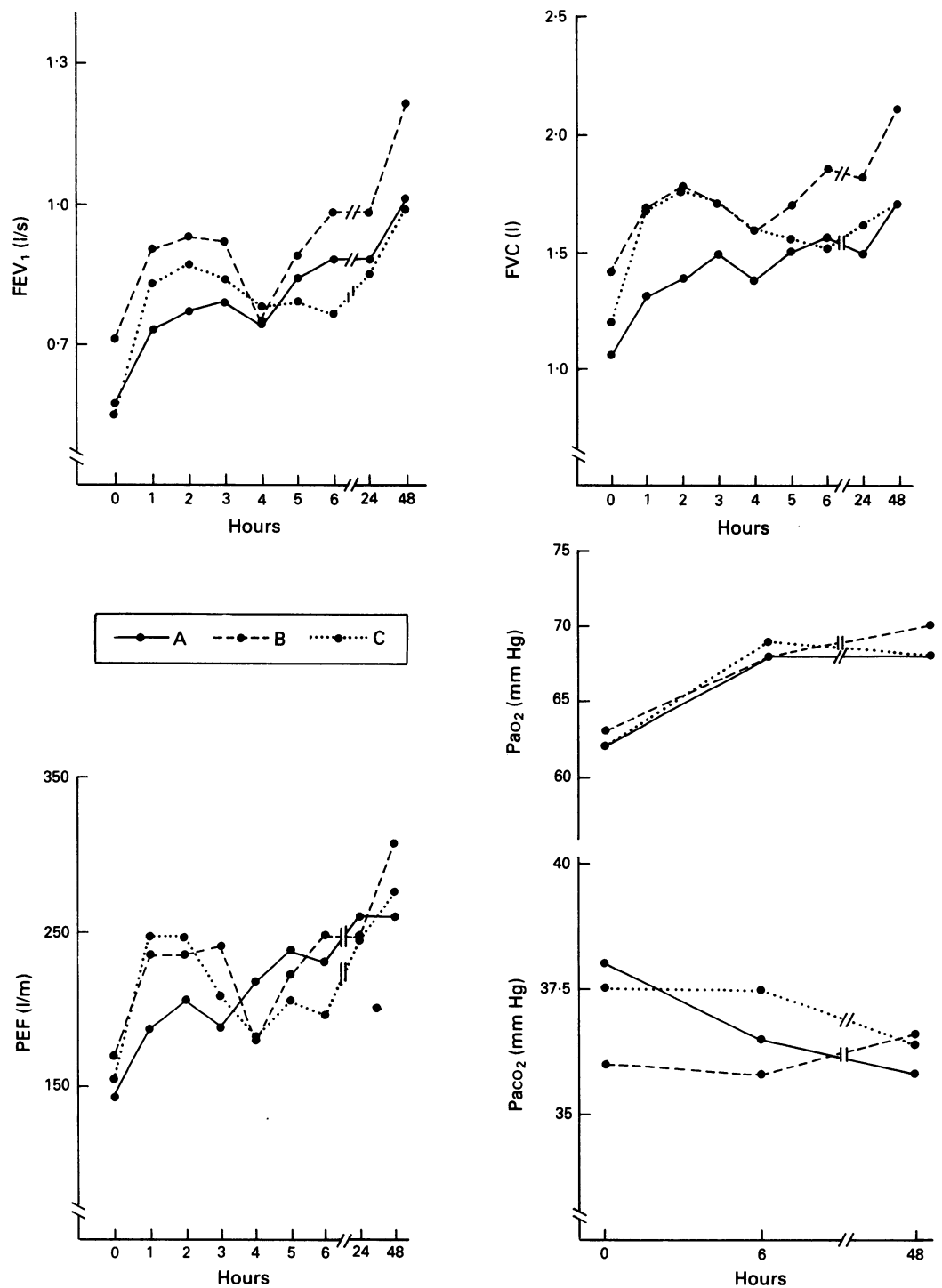
asthma Stein and Cole[8] found no benefit for the early administration of corticosteroids given simultaneously with aerosolised metaproterenol and oral theophylline. They concluded that routine administration of corticosteroids at presentation to such patients may not be necessary.

The present study, carried out in a large number of patients, at first appears to support the view that the rate of recovery is not immediately accelerated by intravenous corticosteroids, even when given in high doses. The evaluation of our results, however, should take into account the possibility that the effect of corticosteroids in some patients was masked by the bronchodilator effect of the concomitant

standard treatment. In an attempt to identify patients in whom treatment with intravenous methylprednisolone may have been effective, we took the analysis further by assessing the possible influence of prior regular treatment with oral corticosteroids, failure of PEF to improve by at least 15% by the third hour of treatment, and a blood eosinophil count above $3.5 \times 10^5/l$ at presentation. Eosinophilia did not significantly influence the recovery of any of the respiratory indices studied. An improvement in PEF was, however, observed in those treated with very high doses of corticosteroids whose PEF had not improved by 15% at 3 hours and in those previously taking oral steroids. These differences did not,
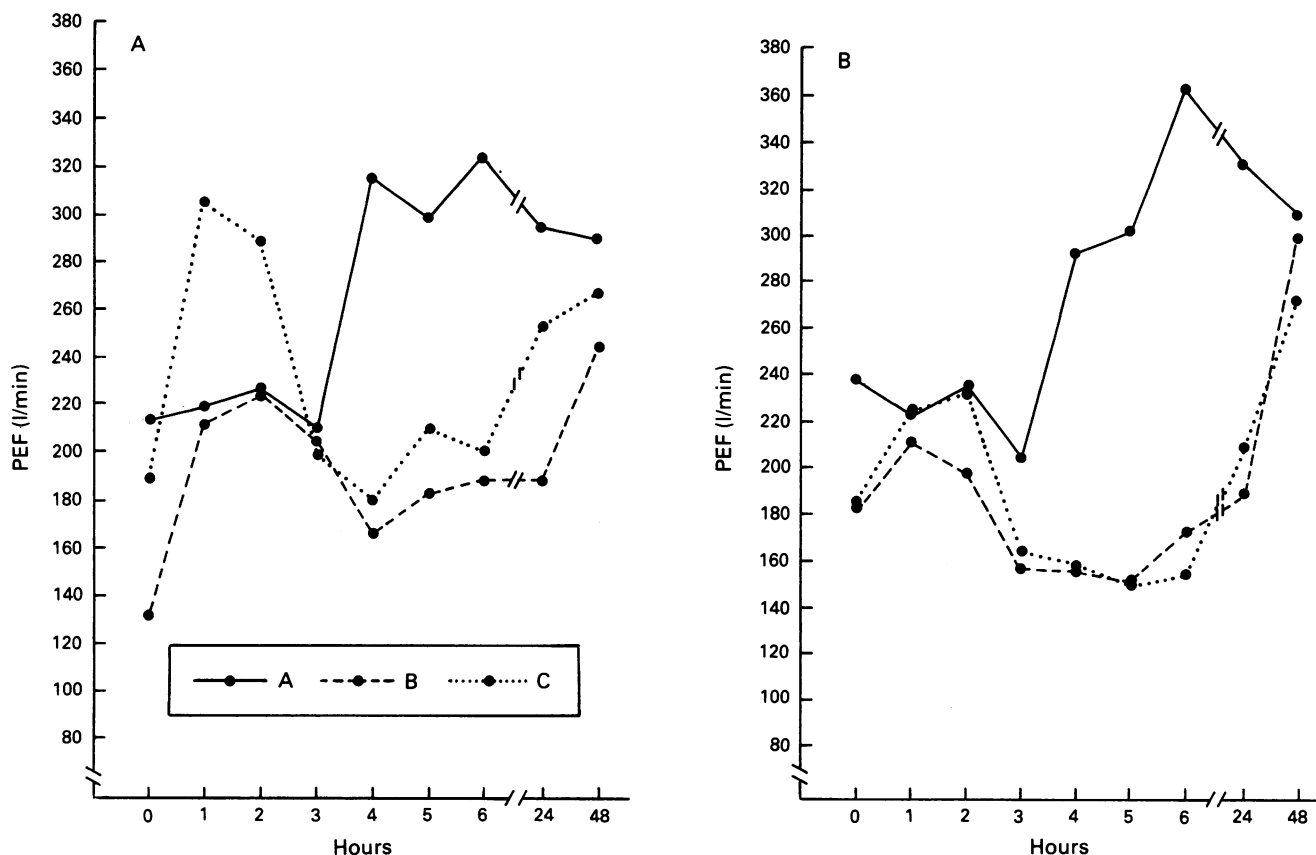
Figure 2   Hourly recordings of peak expiratory flow (PEF) in the patients (A) who failed to show an increase of 15% or more in PEF after three hours of treatment and (B) in patients who were receiving regular treatment with oral corticosteroids when they entered the study.

however, reach statistical significance, probably because of the wide scatter of PEF values.

As pulmonary function in general is at its worst during the first few hours of severe acute asthma and when the risk of death is highest,[19] it is important to achieve a rapid improvement.[20] For that reason, given that corticosteroids do not begin to take effect in acute asthma until at least three hours after administration,[21-25] and that it is impossible to know beforehand which patients will not respond to bronchodilators, it would seem advisable to administer intravenous corticosteroids to all patients with severe acute asthma as soon as possible. The question of how to identify those likely to benefit from corticosteroids remains open.

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