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Original articles

Corticosteroids in acute severe asthma: effectiveness of low doses

S D Bowler, C A Mitchell, J G Armstrong

Abstract

Background **Although the need for corticosteroids in acute severe asthma is well established the appropriate dose is not known.**

Methods **The response to intravenous hydrocortisone 50 mg (low dose), 100 mg (medium dose), and 500 mg (high dose), administered every six hours for 48 hours and followed by oral prednisone, was compared in patients with acute asthma in a double blind randomised study. After initial emergency treatment with bronchodilators subjects received oral theophylline or intravenous aminophylline and nebulised salbutamol four hourly. Patients were given low, medium, or high doses of intravenous hydrocortisone and then 20, 40, or 60 mg/day respectively of oral prednisone with a reducing regimen over the following 12 days. Beclomethasone diproprionate, 400 μg twice daily by metered dose inhaler, was also started. Peak expiratory flow (PEF), forced expiratory volume in one second (FEV_1), and visual analogue dyspnoea scores (VAS) were recorded daily in hospital and PEF and VAS twice daily after discharge for a total of 12 days.**

Results **The 66 subjects (40 female) who completed the study had a mean (SD) age of 31(14) years. On presentation mean (SD) FEV_1 % predicted in the low (n = 22), medium (n = 20), and high dose (n = 24) groups was 17(13), 19(12), and 19(11) and after emergency bronchodilator treatment 32(20), 30(12), and 36(13). After 24 hours of treatment the respective post-bronchodilator FEV_1 % predicted values were 62(22), 62(23), and 65(28) compared with 71(24), 69(22), and 71(24) after 48 hours. No significant difference between the groups was detected. PEF and VAS improved with treatment over the 12 days but was not influenced by steroid dose.**

Conclusions **Hydrocortisone 50 mg intravenously four times a day for two days followed by low dose oral prednisone is as effective in resolving acute severe asthma as 200 or 500 mg of hydrocortisone followed by higher doses of prednisone.**

Department of Respiratory Medicine, Mater Hospital, Brisbane, Queensland 4101, Australia
S D Bowler

Department of Respiratory Medicine, Princess Alexandra Hospital, Brisbane, Queensland 4102, Australia
C A Mitchell
J G Armstrong

Reprint requests to:
Dr S D Bowler.

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Although corticosteroids are considered essential treatment for acute severe asthma[1] and widely prescribed, there have been remarkably few studies on how the drugs should be given in this condition. In particular, considerable uncertainty remains about the most appropriate dose.

The widely accepted regimen of intravenous hydrocortisone 200–300 mg every six hours appears to be based on work by Collins *et al* in 1975.[2] On the basis of earlier descriptive work on cortisone metabolism in steroid dependent asthmatic patients during acute severe episodes,[3] Collins suggested that doses of corticosteroids equivalent to hydrocortisone 300 mg four times a day would achieve "therapeutic" serum concentrations. The authors found that higher doses were no more effective,[4] and this has been confirmed in other studies.[5–7] Few studies have explored the response to lower doses.[8 9]

Apart from the problem of cost, high doses of corticosteroids may cause more steroid related side effects than low doses. Shee,[10] for example, suggests that a high total dose may be a factor in acute myopathy in patients with acute severe asthma.

We have therefore compared, in a double blind randomised trial, three doses of intravenous hydrocortisone six hourly in patients with acute severe asthma. The doses were 50 mg (low dose, equivalent to prednisone 50 mg a day), 200 mg (medium dose), and 500 mg (high dose). Parenteral treatment was followed by matched low, medium, or high doses of oral prednisone (20, 40, or 60 m daily), which were then tapered over 12 days.

Methods

We studied subjects with acute severe asthma presenting to the accident and emergency departments of two general hospitals. Subjects were aged 18–65 years with an unequivocal history of asthma and previously or subsequently showed short term variability in forced expiratory volume in one second (FEV_1) of at least 15%. Patients with complicating factors such as a pneumothorax or consolidation on the chest radiograph, asthma that warranted admission to the intensive care unit, or other major illness were excluded, as were subjects who had been taking more than 10 mg prednisone a day before admission. The study received the approval of the ethics committee and all subjects gave informed consent.

The patients assessed the severity of their dyspnoea on a 100 mm visual analogue scale[11] (100 mm = no symptoms; 0 mm = maximum symptoms) and recorded peak expiratory flow

(PEF) and FEV_1. A detailed history of the patient's asthma and treatment was taken.

After treatment in the accident and emergency room with 10 mg of nebulised salbutamol and intravenous aminophylline (5 mg/kg or 2·5 mg/kg for patients taking oral theophylline), those who required admission were randomised to receive intravenous hydrocortisone every six hours in doses of either 50 mg (low dose), 200 mg (medium dose), or 500 mg (high dose). Treatment was given in a double blind fashion. Four hourly nebulised salbutamol and parenteral aminophylline or oral theophylline (with the dose adjusted to maintain a serum concentration of 10–20 mg/l) were also administered.

After 48 hours hydrocortisone was stopped and oral prednisone started as a single daily dose. Subjects in the low dose hydrocortisone group were given 20 mg (reducing to 5 mg over 12 days); those in the medium dose hydrocortisone group 40 mg (reducing to 10 mg); and those in the high dose hydrocortisone group 60 mg (reducing to 20 mg). Medication was dispensed double blind in prepacked lots containing 5 mg prednisone and identical placebo tablets. All subjects received metered aerosol beclomethasone, 400 μg twice daily.

Subjects considered unsuitable for the change to oral corticosteroid at 48 hours were regarded as treatment failures. The timing of discharge was at the discretion of individual physicians, as were the dose and formulation of inhaled β agonists and theophylline; most patients were given oral theophylline and salbutamol by metered inhaler after discharge.

FEV_1 and PEF before and after bronchodilator and visual analogue scale score for dyspnoea were measured once daily by the investigators over the initial 48 hours. In addition, subjects kept diary cards, recording twice daily PEF before and after bronchodilator and visual analogue scale score for wheeze, dyspnoea, and disturbance of sleep. Subjects were asked to maintain diary cards for a total of 12 days.

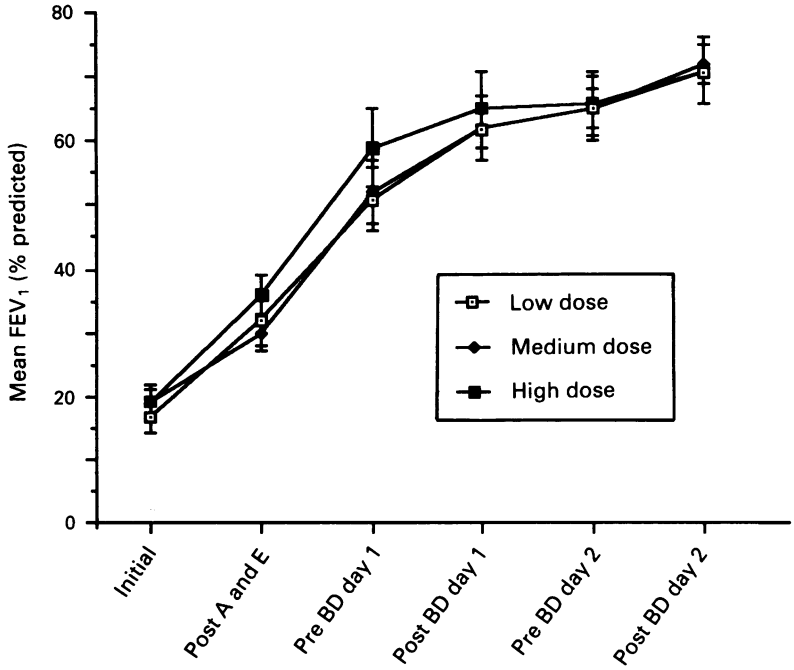

Figure 1 Mean (SE) FEV_1 as a percentage of the predicted value before and after bronchodilator treatment (BD) in the accident and emergency department (A and E) and for the next two days for the low, medium, and high dose groups (n = 20, 22, and 24). There was no difference between treatment groups at any stage. Except for post BD day 1 – pre BD day 2, all values within each treatment group are significantly different from the preceding and subsequent measurements (p < 0·01).

Details of patients in the three groups

	Steroid dose		
	Low	*Medium*	*High*
Number	22	20	24
Age (mean (SD) y)	31 (15)	33 (12)	29 (14)
Male (%)	38	35	30
Current smokers (%)	14	25	13
Inhaled steroids (%)	32	40	40
Low dose oral steroid (< 10 mg/day for over 1 month)	2	1	2
Two or more admissions in last year (%)	23	15	33
Duration of "attack"			
⩽12 hours (%)	18	30	33
⩾3 days (%)	55	30	21
Last undisturbed sleep ⩾7 days ago (%)	55	40	54

POWER CALCULATION

To detect a 0·5 l difference in FEV_1 between the groups receiving high, medium, and low doses after 48 hours of treatment with a power of 80% and an α of 0·05, a total of 75 patients would be needed. In the event, although 76 were enrolled, data on only 66 were analysable.

ANALYSIS

The effect of corticosteroid treatment group on FEV_1, PEF, and visual analogue scale score was determined for each index by means of analysis of variance. Paired *t* tests were used for comparisons within treatment groups between times.

Results

Seventy six subjects were randomised to receive low, medium, or high dose hydrocortisone. Ten subjects were excluded after randomisation. One subject from the medium dose group required intensive care treatment, five subjects improved rapidly and requested discharge before 48 hours (two low dose group, three medium dose group), and four were excluded for violations of protocol (1 high dose (failure to collect data) and three from the low dose group (failure to collect data and incorrect steroid dose)). No patient required intravenous treatment beyond 48 hours.

Of the 66 subjects who completed the study, 22, 20, and 24 were in the low, medium and high dose group respectively. The characteristics of the three groups were similar (table).

FEV_1 % predicted improved with treatment (fig 1). Mean (SD) values at presentation were 17 (13), 19 (12), and 19 (11) in the low, medium, and high dose groups. After treatment in the accident and emergency room the values (% predicted) were 32 (20), 30 (12), and 36 (15). After 24 hours of treatment the respective postbronchodilator values were 62 (22), 62 (23), and 65 (28) and at 48 hours 71 (24), 72 (15), and 71 (26).

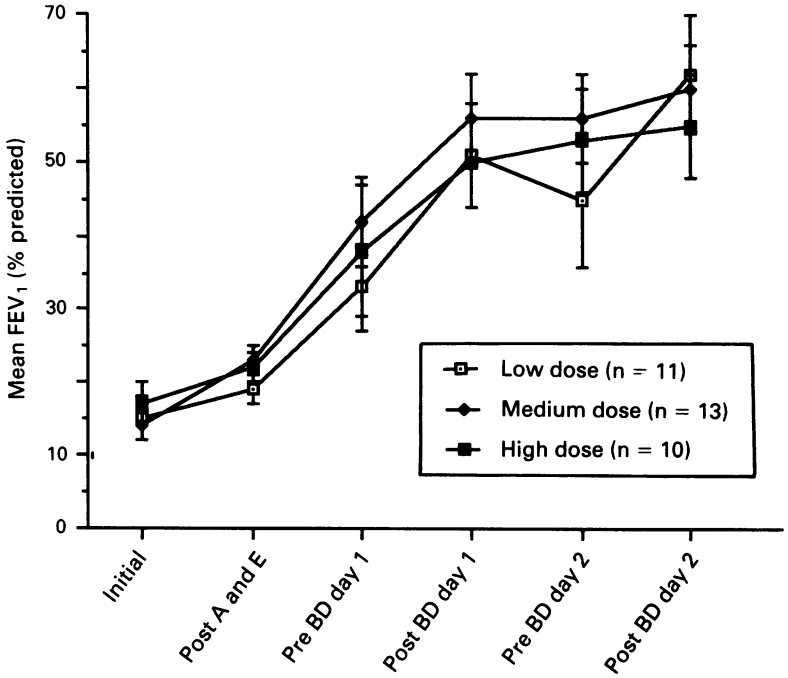

Figure 2 Mean (SE) FEV_1 as a percentage of the predicted value before and after bronchodilator treatment (BD) for the low, medium, and high dose groups in subjects whose FEV_1 after initial treatment in the accident and emergency department (A and E) was less than 30% (n = 11, 13, and 10). There was no difference between treatment groups at any time. Except for post BD day 1—pre BD day 2 all values within each treatment group are significantly different from the preceding and subsequent measurements ($p < 0.01$).

When the 34 subjects whose FEV_1 after treatment in the accident and emergency room was less than 30% predicted (mean 21% (6%)) had their data analysed separately, there were still no differences related to treatment. At 48 hours (after salbutamol) FEV_1 was 62 (27), 60 (22), and 55 (22) % predicted for the low (n = 11), medium (n = 13), and high dose (n = 10) group respectively (fig 2).

Although the study had planned to measure PEF and visual analogue scale score for 14 days, dropout rates were high and by day 12 only 40 patients (67% of original group) were still recording values—13 (59%) in the low dose, 15 (75%) in the medium dose, and 12 (50%) in the high dose group. Morning prebronchodilator PEF (fig 3) improved rapidly after admission, most of the change occurring in the first two days. A trend towards a higher PEF in patients who received the higher dose of prednisone appeared towards the end of the study but the difference did not reach statistical significance. On day 12, mean (SD) morning prebronchodilator PEF values (% predicted) were 78 (27), 78 (27), and 95 (33) in the low, medium, and high dose groups. Mean afternoon postbronchodilator values showed no such trend, mean (SD) % predicted being 87 (31), 102 (24), and 99 (17) in the three groups.

No effect of medication dose on daily variability in PEF—that is, (best PEF − worst PEF)/best PEF)—was observed, mean (SD) % in the low, medium, and high dose groups being 10 (18), 27 (27), and 26 (54).

Corticosteroid dose did not affect subjective perception of asthma, which improved rapidly after admission (fig 4). The mean (SD) visual analogue scale dyspnoea scores before treatment were 18 (20), 31 (21), and 26 (19) mm in the low, medium, and high dose groups and 65 (28), 67 (24), and 70 (23) mm after initial treatment in the accident and emergency department. On the afternoon of the second day of hydrocortisone treatment the visual analogue scale scores were 84 (24), 92 (16), and 88 (15) mm in the low, medium, and high dose groups and in the afternoon after 12 days of treatment 85 (25), 92 (19), and 96 (8) mm.

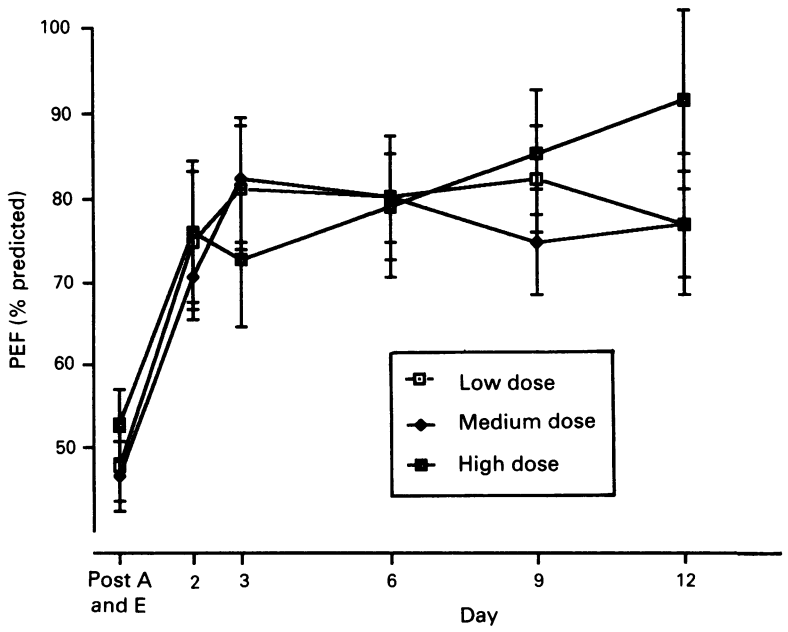

Figure 3 Mean (SE) peak expiratory flow (PEF) after initial treatment in the accident and emergency department (A and E) and before bronchodilator each morning for 12 days. There was no significant difference between treatment groups at any time. For all three groups post A and E PEF is significantly different from all subsequent values ($p < 0.05$); day 2 values are significantly different from day 6 and subsequent values; otherwise no significant time effect is present.

Discussion

In this study of patients with acute severe asthma we have been unable to show any difference in the rate of recovery between subjects given low, medium, and high doses of hydrocortisone. The low dose of hydrocortisone (50 mg every six hours) is equivalent to 50 mg of prednisone a day and the medium dose (200 mg every six hours) is a commonly used inpatient parenteral dose, whereas the high dose (500 mg every six hours) is an empirical high dose. Neither perception of breathlessness (visual analogue scale), nor objective measures (FEV_1, PEF) were influenced by the dose of hydrocortisone. No trend was evident between drug doses at 48 hours. Although we cannot definitely exclude a type II error, it seems unlikely that larger groups of patients would change the results.

Apart from documenting changes over an initial two days, the study attempted to measure the additional effect of varying doses of prednisone over the following 12 days. Although interpretation is limited by the number of subjects who failed to complete their records, there was a trend favouring the group having the highest dose of steroid by day 12 for morning prebronchodilator peak flow readings—but not for afternoon post-treatment values.

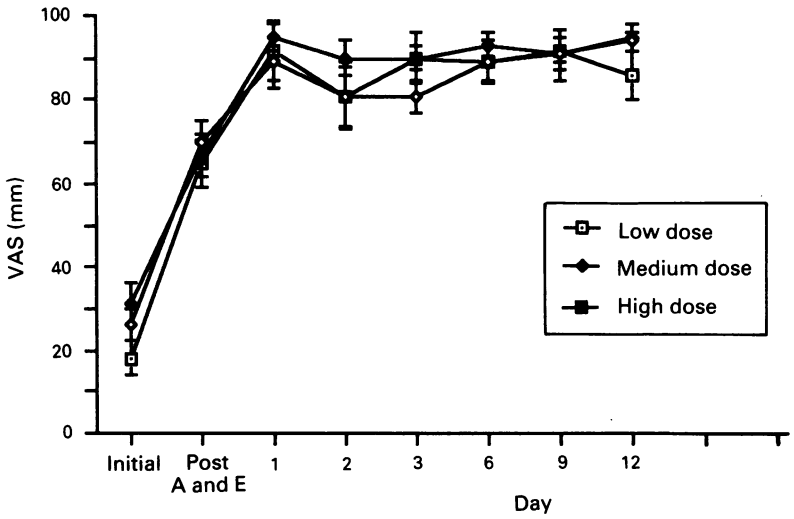

Figure 4 Mean (SE) visual analogue score (VAS) for breathlessness initially, after treatment in the accident and emergency department (A and E), and after bronchodilator on subsequent afternoons. For all three groups initial VAS is significantly different from post A and E ($p < 0.001$), which differs significantly from subsequent values ($p < 0.001$); otherwise no significant time or dose effect is present.

Although our subjects had severe obstruction on presentation, with a mean (SD) initial FEV_1 of 18% (12%) and 33% (16%) predicted after treatment in the accident and emergency department, conceivably patients with less severe asthma who had not in fact needed steroids obscured an effect of dose. The lack of any dose effect (or trend toward any effect), however, in the subset of patients with more severe asthma whose FEV_1 was less than 30% after treatment in the accident and emergency department (mean initial FEV_1 15% (9%); after treatment 21% (60%)) suggests that this is not the case.

Only five of our subjects were taking oral corticosteroids at the time of admission—in each case less than 10 mg of prednisone a day for more than a month. The conclusions from this study may not be applicable therefore to subjects who have been recently taking larger doses of steroid.

This study shows that improvement in airway function in acute severe asthma is rapid when measured by PEF and symptoms—most of the recovery occurring within the first 48 hours. This is in agreement with the findings of other investigations.[4,9]

In interval (non-acute) asthma airway obstruction is sensitive to small changes in steroid dose[12–14] and a maximal effect may be achieved with 30 mg prednisolone daily.[15] In acute severe asthma different, as yet poorly understood, conditions prevail and, although steroids are of value,[16] the evidence is less compelling and data showing a clear dose-response effect are few.

Most comparative dose studies have investigated regimens with doses of 800 mg or more of hydrocortisone (or equivalent) a day; most have shown no benefit from the higher doses.[4–7] Only one study, in 1983,[8] with only eight subjects in each arm, suggested that 160 mg methylprednisolone daily (equivalent to 800 mg of hydrocortisone daily) was superior to 40 mg daily (equivalent to 200 mg hydrocortisone); we are unable to reproduce this finding.

Webb[9] found a dose-response relationship in a study investigating lower doses in outpatients (10 subjects studied during three separate exacerbations) with less severe asthma who were treated with lower doses of steroid. They received oral prednisolone 14, 28, and 42 mg daily. His (oral) high dose is nearly equivalent to the low dose of intravenous hydrocortisone in our study. Our dose ranges do not overlap, and our results are not inconsistent with his finding of a dose effect below a total daily prednisone dose of 42 mg.

Although occasional patients with acute severe asthma may require higher doses of hydrocortisone or prednisolone our work suggests that an initial daily dose of 200 mg of hydrocortisone (equivalent to prednisone 50 mg/day) is adequate for most patients. High doses, apart from being more expensive, may be associated with more side effects[10] and for most patients are unnecessary.

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