Intravenous β agonist in severe acute asthma

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Abstract

Study objective—To determine whether salbutamol is more effective in treating severe asthma when given intravenously or by inhalation.

Design—Randomised trial of short term response to intravenous versus nebulised salbutamol in acute severe asthma.

Setting—District general hospital (secondary care centre).

Participants—76 patients aged 16-70 admitted to hospital with acute severe asthma (peak expiratory flow rate <50% of predicted) during study period. Five withdrawn because of adverse effects of treatment or non-response. Of remaining 71, 34 allocated to nebuliser group and 37 to intravenous treatment group. Patients with history of cardiovascular disease or recent corticosteroid or intravenous bronchodilator treatment excluded. Admission characteristics similar in the two groups.

Interventions—All patients given 5 mg nebulised salbutamol on admission before randomisation plus 200 mg hydrocortisone bolus intravenously and 35% inspired oxygen throughout. Nebuliser group received two more 5 mg doses of nebulised salbutamol at 30 minutes and 2 hours; intravenous group received 4 hours' continuous salbutamol infusion (12 μ g/min) starting at 30 minutes plus supplementary intravenous potassium chloride. No other bronchodilators used.

Endpoint—Change in peak expiratory flow rate over 4 hours.

Measurements and main results—Peak expiratory flow rate improved more in intravenous group (25.2%) than in nebuliser group (14.3%) ($p < 0.01$, 95% confidence interval 2.4 to 19.1%). Tachycardia caused two withdrawals from intravenous group; non-response caused three withdrawals from nebuliser group.

Conclusions—Intravenous salbutamol is more effective than nebulised salbutamol in acute severe asthma but may have unacceptable cardiovascular effects.

Introduction

One of the controversies in the hospital treatment of severe acute asthma concerns the route of administration of the bronchodilator drug.¹ Studies have investigated the use of intravenous β agonists and reported that this route produces the same degree of bronchodilatation as inhaling a nebulised aerosol.²⁻⁵ These studies, however, either had low power with consequent type II error or investigated patients who had mild but not severe asthma. The present study was designed to have adequate power to detect a clinically useful difference between peak flow rates after treatment with intravenous and nebulised salbutamol and investigated only those patients admitted to hospital because of severe asthma.

Patients and methods

Patients aged between 16 and 70 years and admitted to hospital because of severe acute asthma were studied. Any patient who had a history of cardiovascular disease or who had received corticosteroid or intravenous bronchodilator treatment before admission was excluded. On admission the pulse rate, peak flow rate (the best of two attempts with a Wright peak

flow meter), and arterial blood gases were measured. At the same time all patients were given 5 mg nebulised salbutamol with a Hudson nebuliser driven by oxygen at 6 l/min and an intravenous bolus of 200 mg hydrocortisone. Those whose peak flow rate remained below half of the predicted value 30 minutes after nebulised treatment were randomised, with a sealed envelope system, to receive either intravenous salbutamol or further nebulised salbutamol. No other bronchodilator was used. All were given continuous 35% inspired oxygen.

Those randomised to receive only nebulised treatment inhaled 5 mg salbutamol 30 minutes after the first treatment on admission and again two hours later. The group randomised to receive intravenous treatment was given salbutamol as a continuous infusion in a dose of 12.5 μ g/min starting 30 minutes after admission and lasting for a further four hours. Hypokalaemia may be produced by this treatment, and 2 g potassium chloride was therefore added to the infusion. The pulse rate and peak flow rate were monitored hourly for four hours.

The peak flow response was assessed as the change in peak flow rate (PFR) expressed as the percentage of the predicted maximal response by the equation: % response = ((PFR after treatment—initial PFR)/(predicted PFR—initial PFR)) $\times$ 100. The number of patients required to give the study adequate power was calculated from the nomogram published by Altman.⁶ We assumed that the standard deviation of the percentage increase in peak flow rate produced by the treatment would be 20%. A minimum of 60 patients would then be required to detect a true difference of 15% between treatments and would give the study a power of 0.85 at the significance level $\alpha = 0.05$. Statistical analysis was carried out with paired and unpaired *t* tests (two tailed).

Results

Of 76 patients studied, five were withdrawn because of either adverse effects or non-response to treatment. Seventy one patients therefore completed the study: 37 received intravenous salbutamol and 34 were treated only with nebulised salbutamol. The two groups were well matched for age, sex, and severity of asthma before treatment (table I). The peak flow rate

TABLE I—Severity and type of asthma in each treatment group

	Salbutamol treatment	
	Intravenous	Nebulised
No and sex	26M, 11F	23M, 12F
No atopic	9	10
Mean (range) age (years)	37 (16-69)	35 (16-66)
Mean (SD) peak flow rate (l/min):		
On admission	91 (37.2)	111 (53.4)
On discharge	360 (160)	359 (107)
Peak flow rate on admission expressed as % of predicted mean (SD)	20.4 (6.9)	24 (9.1)
Mean (SD) blood gas tension on admission (kPa):		
Oxygen tension	8.8 (1.1)	9.1 (1.2)
Carbon dioxide tension	4.9 (1.0)	4.7 (0.7)

response of 6.3% produced by nebulised salbutamol on admission before randomisation to the different treatments was the same in both groups.

After randomisation the mean percentage response of the peak flow rate was greater in the intravenous group at all times, reaching significance three hours after the start of infusion (table II). At this time the percentage response was 20.7% in the intravenous

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group versus 12% in the nebulisation only group ($p<0.025$). One hour later the response was 25.2% in the intravenous group and 14.3% in those given nebulised treatment ($p<0.01$).

TABLE II—Percentage increase in peak flow rate in each treatment group

Time (h)	Mean (SD) % peak flow rate response (l/min)		Difference (significance)	95% Confidence interval
	Intravenous group	Nebulised group		
0.0	0.0	0.0		
0.5	6.3 (5.9)	6.3 (8.5)	0.0 ($p>0.1$)	-3.5 to 3.6
1.5	13.2 (12.4)	10.9 (13.9)	2.3 ($p>0.01$)	-3.9 to 8.6
2.5	17.3 (15.6)	10.6 (13.3)	6.7 ($p>0.05$)	-0.2 to 13.5
3.5	20.7 (19.8)	12.0 (13.5)	8.7 ($p<0.025$)	0.7 to 16.7
4.5	25.2 (19.9)	14.3 (15.9)	10.9 ($p<0.01$)	2.4 to 19.1

The mean improvement rate in peak flow was 7.8 l/min/hour in the nebulised group and 17.3 l/min/hour in those receiving intravenous treatment.

The mean pulse rate fell in the nebulised group, but tachycardia was prominent in those given intravenous salbutamol (table III). Two patients were withdrawn from the intravenous group. A 19 year old woman complained of headache and palpitation, and her pulse rate was 150 beats/min. Her peak flow rate had improved from 150 l/min to 220 l/min at one hour, when the infusion was stopped. The second patient was a 36 year old woman who also complained of tremor and palpitation; her pulse rate was 160 beats/min. Her peak flow rate had not improved, remaining at the admission value of 60 l/min. Three patients aged 16, 22, and 30 years were withdrawn from the group treated only with the nebuliser because of no bronchodilator response to nebulised salbutamol. One had received 5 mg salbutamol and the others 10 mg before withdrawal. All were then given intravenous aminophylline.

Discussion

Most attacks of severe acute asthma are initially treated with oxygen, nebulised bronchodilator, and corticosteroid. Corticosteroids, however, take some hours to produce a measurable improvement in respiratory function.⁷ The role of intravenous β agonist remains unclear, and we decided to investigate its use because previous work had investigated mainly chronic asthma and small numbers of patients. Hetzel and Clark found that in well controlled asthma intravenous salbutamol had no benefit over nebulised treatment.³ In another trial Lawford *et al* studied severe asthma and failed to detect any difference in bronchodilation after treatment with intravenous and nebulised salbutamol.⁴ The study had, however, a large type II error,⁸ and the patients were investigated for only 45 minutes. Williams and Seaton recommended using intravenous β agonist but investigated only 10 patients and used a small dose of salbutamol.⁹ Our study was designed to include more patients and therefore to be less likely to contain a type II error. The study also excluded patients whose asthma responded rapidly to a single dose of nebulised treatment, for whom treatment with intravenous bronchodilator seemed unnecessary.

Bronchodilator response may be assessed in various ways. Some have expressed the change in peak flow rate in absolute units or as a percentage of the initial value. This may introduce some bias, because a small change in peak flow rate in patients who have severe obstruction results in an apparently greater response. We expressed the change in peak flow rate as a percentage of the predicted maximum response, as this reflects the degree to which the peak flow rate returns

to normal and allows the subjects to be compared independently of their body size and the severity of asthma.¹⁰ Though such an analysis cannot be assumed to control completely for differences in the baseline peak flow rate between groups, the method has been suggested to produce the best assessment from a clinical standpoint.

The optimum infusion rate of intravenous salbutamol in treating acute asthma is not known. May *et al* infused salbutamol in 10 patients who were recovering from an acute attack in doses varying between 4.16 μ g/min and 25 μ g/min.¹¹ They reported that the greatest bronchodilator effect was produced by a dose of 4.16 μ g/min. In patients who have more severe asthma than those studied by May *et al* a larger dose would probably be required. We were anxious to obtain maximum bronchodilatation with as few adverse effects as possible and chose, after a pilot study, a dose of 12.5 μ g/min. At this dose two patients were withdrawn because of tachycardia.

The results, however, showed that the response of the peak flow rate was significantly greater in those given intravenous salbutamol. The reason for the better response achieved by the intravenous route probably lies in the accessibility of the bronchodilator to its site of action. In severe asthma obstruction of the airway is due to a combination of muscle spasm, mucosal oedema, and mucus plugging,¹² and this would diminish access inhaled drug. Though both groups showed an improved peak flow rate after treatment, the percentage improvement in peak flow rate was greater in the intravenous group at all times. It is not possible to explain the difference in the response of the peak flow rate between the two groups by saying that one group had more severe asthma than the other. In both groups the peak flow rate on admission and discharge was very similar (table I). No patient received any other bronchodilator, and all were given the same dose of hydrocortisone.

Intravenous salbutamol may theoretically have a deleterious effect on arterial oxygen gas tension by dilating pulmonary vessels and so perfusing areas of poorly ventilated lung. Others, however, have measured changes in arterial oxygen tension before and after treating severe asthma with intravenous β agonist and reported either no change or some improvement with treatment.^{13,14} We have been able to measure the changes in oxygen tension one hour after treatment in 10 people who had acute asthma, and we have also been unable to detect any significant change. All patients were breathing 35% oxygen. It is therefore likely that either improved ventilatory function or other effects on cardiac output or peripheral vascular resistance offset any effects on the pulmonary vessels.¹⁶

TABLE III—Changes in pulse rate in each treatment group

Time (h)	Mean (SD) pulse rate (beats/min)		Difference (significance)	95% Confidence interval
	Intravenous group	Nebulised group		
0.0	114 (14)	110 (14)	4 ($p>0.01$)	-9 to 4
0.5	105 (14)	101 (17)	4 ($p>0.05$)	-11 to 2
1.5	114 (17)	106 (15)	8 ($p=0.05$)	0 to 14
2.5	113 (17)	101 (14)	12 ($p<0.01$)	5 to 21
3.5	117 (16)	102 (14)	15 ($p<0.001$)	8 to 22
4.5	116 (14)	98 (15)	18 ($p<0.001$)	8 to 21

Treatment with intravenous and perhaps inhaled β agonist requires potassium supplements, as both produce hypokalaemia.^{17,18} We now monitor serum potassium concentrations during the infusion, and values fall in some patients by as much as 0.5 mmol/l.

We are anxious not to dismiss nebulised treatment. Thirty minutes after the initial 5 mg nebulised salbutamol the percentage response of the peak flow rate

was 6.3%. Repeated doses of nebulised salbutamol over the next two hours produced further bronchodilatation, the peak flow rate response rising by 14.3% after four hours. It is therefore important to notice that large doses of nebulised β agonist may be repeated and can produce useful bronchodilatation.

The patient who has acute severe asthma is, however, a medical emergency requiring immediate effective bronchodilator treatment. The intravenous route has perhaps been neglected in this country. This has been shown by a recently published survey of the treatment of severe asthma in the United Kingdom, in which only five of 67 hospital doctors regularly used intravenous β agonist.¹⁹ We believe that intravenous β agonists have a place in treating some severely asthmatic patients. It must be remembered, however, that large doses may have adverse cardiac and metabolic effects, and because of this serum potassium concentrations must be monitored and the treatment probably not used for those who have a history of myocardial disease.

We thank the nursing staff, Professor G S Kilpatrick, Dr I A Campbell, Dr B H Davies, and Dr A P Smith at Llandough Hospital for their support with this study.

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(Accepted 20 May 1988)

Epidemiology of symptomatic infections of the urinary tract in children

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Abstract

The epidemiology of symptomatic infections of the urinary tract in children and the factors that may alter the risk of infection are not well known. Numbers of children aged under 15 discharged from hospitals because of symptomatic infections of the urinary tract during 1978-84 were obtained from the database kept by the Finnish National Board of Health. Information on continuous treatment for recurrent urinary tract infections was obtained from records kept by the Social Insurance Institution on patients receiving free medicines. The yearly rate of attacks of symptomatic infections/1000 girls decreased significantly from 2.67 (95% confidence interval 2.52 to 2.82) in 1978 to 1.88 (1.76 to 2.01) in 1984. In boys the rate also decreased significantly, from 0.85 (0.77 to 0.93) in 1978 to 0.59 (0.52 to 0.66) in 1984. The period prevalence of free treatment/1000 girls decreased significantly from 7.80 (7.55 to 8.05) in 1978 to 5.30 (5.10 to 5.51) in 1984 but did not change significantly in boys.

Although the findings may partly have been caused by changes in policies of admission to hospital, they suggest a decreasing trend in symptomatic urinary tract infections in childhood, which may be associated with changes in the care of infants.

Introduction

Although the epidemiology of asymptomatic bacteriuria in infancy and childhood has been thoroughly studied,^{1,2} little is known about that of symptomatic infections of the urinary tract.³ Stansfeld estimated that roughly 0.17/1000 boys and 0.4/1000 girls required

treatment in hospital for urinary tract infections,⁴ though Winberg *et al* found a significant but unexplained increase in the total number of children admitted to hospital because of symptomatic urinary tract infections during 1952-66.⁵ Susceptibility to infection is poorly understood, and changes in susceptibility with time may point to important environmental or behavioural factors that can alter the risk of infection.

To monitor epidemiological trends we analysed information available nationally on children admitted to hospital with urinary tract infections and on the use of preventive treatment for such infections.

Patients and methods

The Finnish National Board of Health keeps a central database recording the age, sex, and main diagnosis of patients discharged from all hospitals in Finland. From this we compiled figures for children aged under 15 who had been treated for symptomatic urinary tract infections during 1978-84. The data were readily available in the three age groups 0-4, 5-9, and 10-14 for boys and girls separately. Almost all children under the age of 1 are admitted to hospital when they have a symptomatic urinary tract infection and figures for these children were therefore collected separately from the same database. In Finland children receiving prophylactic treatment because of recurrent urinary tract infections are permitted free medicines, and the Social Insurance Institution keeps records of all patients receiving free treatment. From this source we collected information yearly on children receiving continuous treatment for recurrent urinary tract infections.

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