EFFECT OF INTRAVENOUS INJECTION OF SALBUTAMOL IN ASTHMA

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- 1 The effect of i.v. salbutamol was compared with aerosol salbutamol in ten asthmatic patients.
- 2 A cumulative dose of salbutamol (300 μ g) given in three separate injections over 45 min resulted in a mean increase in peak expiratory flow rate (PEFR) of 38.3% and FEV₁ of 36%.
- 3 There was no significant difference in degree of bronchodilatation to the same dose of salbutamol administered intravenously or by aerosol.
- 4 Palpitations, tremor, and postural hypotension were common when the drug was injected intravenously over one minute, but did not occur after aerosol administration.
- 5 It is suggested that salbutamol by intravenous injection is a useful addition to the treatment of acute asthma.

Introduction

In the treatment of the acute attack of asthma, both in domiciliary and hospital practice, a parenteral injection of a bronchodilator may be of great benefit to the patient. For many years subcutaneous adrenaline has been the mainstay of such treatment, or alternatively intravenous or intramuscular theophylline preparations. Cardiovascular side-effects can be a problem with both these groups of drugs as they are non-selective. More recently, intramuscular and subcutaneous orciprenaline became available, and following this subcutaneous terbutaline, a selective β_2 -adrenoceptor stimulant.

In the present study we assessed the effect of i.v. bolus injections of salbutamol, another widely used β_2 -adrenoceptor stimulant. The dose-response relationship to i.v. salbutamol was assessed in ten asthmatic patients and compared with that to aerosol salbutamol, in the same patients.

Methods

Ten convalescent asthmatic patients who responded to an inhalation of salbutamol with an increase in peak expiratory flow rate (PEFR), forced expiratory volume in 1 s (FEV₁), and forced vital capacity (FVC) of at least 20%, were

studied (Table 1). One patient, in addition to asthma, suffered from chronic bronchitis. Patients with known cardiovascular disease were excluded. All patients were being treated with bronchodilator drugs and these were discontinued from the evening prior to the study. Some patients were also receiving corticosteroids or disodium cromoglycate and these were continued. After a full explanation of the procedures to be carried out, the informed consent of each patient was obtained.

The patients were studied reclining on a couch. PEFR was measured using a Wright peak flow meter (Airmed Ltd) and FEV₁ and FVC with a dry spirometer (Vitalograph). The electrocardiogram was monitored continuously using standard limb leads and an oscilloscope, and the blood pressure was measured indirectly by sphygmomanometry. A 12-lead electrocardiogram was recorded before and after each study.

Each patient was studied on two consecutive days. In one study the dose-response curve to i.v. bolus injections of salbutamol was plotted, and in the other the dose-response curve to aerosol salbutamol was obtained. The treatment order was randomized, half the patients receiving i.v. drug on the first day and half aerosol.

On each study day, baseline recordings of PEFR, FEV₁, FVC, heart rate and blood pressure

were obtained prior to administration of the drug. On the day of i.v. administration, a cannula was inserted into a vein in the dorsum of the hand prior to baseline recordings. When steady baseline recordings had been obtained, salbutamol, diluted in normal saline to a concentration of 50 µg/ml, was injected via the cannula. Bolus injections were given over 1 min, commencing with a dose of 50 µg (= 1 ml) and increasing by increments, each one 50 µg larger than the previous, i.e. 50, 100, 150 µg etc., every 15 min until either lung function measurements showed no further improvement or cardiovascular effects were judged great enough to terminate the study, or an increment of 450 µg was reached (a cumulative dose of 2,250 µg).

On the day of the aerosol study, steady baseline readings were obtained. Salbutamol was then given from a pressurized aerosol (Ventolin, Allen & Hanburys: 100 µg per dose) in doses of 100, 200, 400 and 800 µg at 15 min intervals.

The physiological data were recorded 1 and 15 min after each i.v. bolus, and 15 min after each inhalation. Following the 15 min readings the next incremental dose of i.v. or aerosol salbutamol was given.

The significance of the difference between mean responses was analysed using Student's paired *t*-test.

Results

In the i.v. study, six patients showed no further improvement in FEV₁ and PEF_R after the 300 µg increment (three patients) or the 350 µg increment (three patients), i.e. cumulative doses of 1,050 and 1,400 µg respectively. In one patient (C.B.) following the 250 µg increment of salbutamol (cumulative dose 750 µg) there was a rise in heart rate from 90 to 180 beats/min following injection, and this was associated with a fall in blood pressure from 110/60 mmHg to 100/40 mmHg at 1 min following injection. The study was therefore terminated at this dose, and 15 min later the heart rate was 120 beats/min and blood pressure 100/50 mmHg. For the remaining three patients the full number of increments up to 450 µg (cumulative dose 2,250 µg) was given before the lung function measurements showed no further improvement.

All patients received all the doses of inhaled salbutamol.

Table 2 shows PEF_R, FEV₁ and FVC values obtained expressed as mean percentage increase above baseline values (± 1 s.e. mean), and heart rate, systolic and diastolic blood pressure as mean absolute change from baseline values (± 1 s.e. mean) for i.v. injection. Table 3 expresses the same data obtained after aerosol salbutamol in the

Table 1 Patient data

Patient number	Age (years) and Sex	Weight (kg)	Pulmonary function tests (ATPS)				Baseline FEV ₁ (litres)		Baseline PEFR (litres/min)	
			Predicted		PEFR (litres/min)	i.v.	Aerosol	i.v.	Aerosol	
			FEV ₁ (litres)	FVC (litres)						
1	44 F	49.9	2.45	3.1	457	1.1	1.0	125	140	
2	42 F	80.3	2.5	3.1	462	1.15	1.25	105	155	
3	31 M	76.5	3.7	4.4	625	1.5	1.1	225	185	
4	41 F	57.2	2.5	3.05	463	1.4	1.25	290	245	
5	40 M	85.7	3.8	4.65	620	2.6	2.8	365	320	
6	58 F	73.0	2.4	3.1	427	1.25	1.4	345	340	
7	23 F	52.6	2.85	3.35	507	1.95	2.3	220	265	
8	32 M	59.4	4.15	4.95	632	1.25	1.3	180	205	
9	66 F	58.5	1.9	2.55	402	1.0	0.75	185	170	
10	43 M	64.0	3.65	4.6	615	0.95	1.2	255	245	

Table 2 Physiological data recorded 1 and 15 min after i.v. salbutamol injections (mean $\pm$ 1 s.e. mean, $n = 10$)

Incremental dose (μ g)	Cumulative dose (μ g)	Time after injection (min)	% increase FEV_1 above baseline	% increase FVC above baseline	% increase PEF above baseline	Heart rate increase (beats/min)	Change in systolic BP (mmHg)	Change in diastolic BP (mmHg)
50	50	1	24.0(2.7)	11.1(4.0)	22.8(7.3)	7.0(3.2)	2.1(4.2)	-3.6(2.1)
		15	8.7(4.1)	10.4(3.4)	10.1(7.2)	-0.8(1.9)	-1.7(2.5)	-2.8(2.4)
100	150	1	36.3(4.3)	23.3(5.3)	45.9(11.7)	15.3(2.6)	12.1(4.1)	-8.8(2.8)
		15	23.2(6.5)	18.0(6.8)	26.4(10.0)	1.6(2.1)	1.1(4.2)	-1.7(3.0)
150	300	1	52.0(5.9)	35.3(8.6)	64.3(18.1)	22.7(4.4)	10.0(7.3)	-10.0(1.7)
		15	36.0(6.1)	23.1(5.5)	38.3(7.9)	6.8(2.2)	0.0(5.1)	-8.1(3.1)
200	500	1	55.1(6.9)	36.0(9.8)	65.8(20.5)	28.8(3.7)	7.8(6.1)	-15.0(3.4)
		15	40.4(7.0)	29.6(6.6)	48.8(14.0)	11.6(3.2)	-2.8(3.9)	-12.8(4.4)
250	750	1	56.7(8.6)	37.7(10.2)	66.2(17.6)	36.6(6.9)	7.8(5.4)	-17.2(2.9)
		15	48.7(8.8)	34.2(9.4)	55.2(18.0)	13.6(3.2)	0.6(4.1)	-7.2(2.2)
300	1050	1	59.3(12.1)	43.2(11.0)	72.9(22.2)	30.7(5.1)	5.0(6.0)	-12.5(2.5)
		15	51.4(9.6)	38.6(7.9)	57.2(17.0)	12.2(2.6)	-1.9(6.2)	-11.3(3.9)
350	1400	1	68.1(15.8)	53.3(13.3)	74.8(14.3)	33.6(5.6)	1.0(5.8)	-18.0(3.4)
		15	50.8(12.8)	49.1(9.9)	50.3(7.9)	6.0(2.7)	-3.0(3.0)	-5.0(5.2)

Table 3 Physiological data recorded 15 min after inhalation of salbutamol (mean $\pm$ 1 s.e. mean, $n = 10$)

Incremental dose (μ g)	Cumulative dose (μ g)	Time after inhalation (min)	% increase FEV_1 above baseline	% increase FVC above baseline	% increase PEF above baseline	Heart rate increase (beats/min)	Change in systolic BP (mmHg)	Change in diastolic BP (mmHg)
100	100	15	37.7(8.5)	24.1(6.2)	41.4(7.8)	3.8(2.5)	-3.8(3.8)	-5.6(2.9)
200	300	15	48.9(9.6)	31.5(7.3)	55.9(10.8)	0.6(2.2)	-2.5(2.9)	-1.0(2.2)
400	700	15	60.8(10.6)	34.3(8.1)	63.8(12.8)	-2.2(2.9)	-2.5(5.1)	-2.5(1.9)
800	1500	15	64.1(11.1)	39.2(8.9)	71.9(13.4)	-2.6(3.5)	1.5(3.7)	-2.0(1.9)

Figure 1 Percentage change (mean $\pm$ s.e. mean, $n = 10$) in FEV₁ (a) and FVC (b) at 15 min with increasing cumulative dose of salbutamol by injection (●) and aerosol (○).

Figure 2 Change (mean $\pm$ s.e. mean, $n = 10$) in PEFR (a) and heart rate (b) at 15 min with increasing cumulative dose of salbutamol by injection (●) and aerosol (○).

Figure 3 Change (mean $\pm$ s.e. mean, $n = 10$) in blood pressure (a systolic; b diastolic) at 15 min with increasing cumulative dose of salbutamol by injection (●) and aerosol (○).

Figure 4 Increase (mean $\pm$ s.e. mean, $n = 10$) in heart rate at 1 min (■) and 15 min (□) after i.v. injection of salbutamol.

same patients. Figures 1, 2 and 3 show change in FEV₁ and FVC; PEFR and heart rate; systolic and diastolic blood pressure, 15 min after both i.v. and inhaled routes of administration. The dose shown is the calculated cumulative dose obtained by summing the incremental doses given to that point.

It can be seen that with i.v. administration there is a progressive rise in PEFR, FEV₁, and FVC measured at 15 min following each injection. The mean rises following the 150 µg increment (cumulative dose 300 µg) were PEFR 38.3%; FEV₁ 36%, and FVC 23.1%. These mean rises were all significantly greater than the rises seen at the two lower incremental doses, 50 and 100 µg ($P < 0.01$). Further increases in the dose produced small additional improvements in mean spirometric measurements, but these were not significantly greater than the values stated for the cumulative dose of 300 µg. At 1 min the mean increase in PEFR, FEV₁ and FVC was significantly higher than that seen at 15 min at all doses studied.

Following aerosol administration there was also a progressive improvement in PEFR, FEV₁ and FVC, the increase between each increment being significant ($P < 0.05$). The mean rises in PEFR, FEV₁ and FVC were higher following aerosol as compared to i.v. administration at comparable cumulative doses but these differences were not statistically significant.

Figure 4 shows the rise in heart rate 1 min and 15 min following each incremental injection. The rise at 1 min was significant at all doses ($P < 0.05$). At 15 min there was a significant rise following the 200 µg incremental dose (cumulative dose 500 µg) and subsequent increments ($P < 0.01$). At all incremental doses the difference between the 1 and 15 min values was significant. The falls in diastolic blood pressure seen at 1 and 15 min were not significantly different. There was no significant change in systolic blood pressure after any i.v. dose.

Following aerosol administration of salbutamol, no significant change was seen in heart rate or blood pressure at any dose given.

Palpitations occurred within 1 min after i.v. injection in four out of the ten patients at and above incremental doses of 100 to 150 µg (cumulative dose 150-300 µg). These disappeared rapidly within 2 to 3 minutes. Tremor was noted in four patients at and above an incremental dose of 250 µg (cumulative dose 750 µg). Again this was a transient phenomenon and had disappeared by 15 minutes. Patients reported that the sensation of palpitation was one of increased force of the heart beat. No palpitations or tremor was seen after aerosol dosage up to an incremental

dose of 800 µg (cumulative dose 1,500 µg). Apart from sinus tachycardia no abnormality was noted in the electrocardiogram.

Discussion

Previous reports on i.v. infusion of salbutamol for periods of 5-7 min have shown it to be an effective bronchodilator (Paterson, Courtenay Evans & Prime, 1971; Svedmyr & Thiringer, 1971), approximately equipotent with isoprenaline but 7-10 times less potent in causing tachycardia. In the present study, we report the use of single bolus injections of salbutamol as opposed to infusion, as this would be a more useful mode of administration, especially in domiciliary practice.

Inspection of the spirometric data at 15 min following each injection showed that although the mean rises were less than at 1 min they were still significant (Table 2). In addition a progressive rise in the 15 min heart rate was seen with each increment (Figure 4). Thus the duration of action of an i.v. bolus persists for longer than 15 min, although the effect has diminished significantly at this time. In order to compare the i.v. and aerosol routes therefore the spirometric responses at 15 min were plotted for the cumulative rather than incremental doses (Tables 2 and 3, Figures 1, 2 and 3).

When the spirometric readings for cumulative i.v. and aerosol doses are compared, it can be seen that the mean readings are higher for the aerosol route but the difference is not statistically significant (Figures 1 and 2).

It has been shown that approximately 90% of an aerosol dose is swallowed and only 10% reaches the lung to produce bronchodilatation (Dollery, 1973). Thus aerosol salbutamol appears ten times more potent than by the i.v. route. We presume this reflects the very high surface concentrations in the bronchial mucosa and bronchial smooth muscle following inhalation when the drug reaches the bronchial mucosa from the airway, as opposed to the situation where a much lower concentration is presented to the mucosa after i.v. injection. This would also suggest that the duration of action should be considerably shorter after i.v. administration, and indeed in the present study the effect has fallen significantly at 15 min whereas aerosol salbutamol has been shown to have a much longer duration of action (Kennedy & Simpson, 1969; Warrell, Robertson, Newton Howes, Conolly, Paterson, Beilin & Dollery, 1970; Walker, Evans, Richards & Paterson, 1972). In addition even at the highest aerosol dose, 800 µg increment (1,500 µg cumulative dose), no cardiovascular

changes were seen. This confirms the more selective action of the drug when given by aerosol.

Following i.v. injection, the major bronchodilator effect occurred after an incremental dose of 150 μ g, i.e. a cumulative dose of 50 + 100 + 150 = 300 μ g given over 45 minutes. This was associated with marked tachycardia (mean 22.7 beats/min) 1 min after the injection of the 150 μ g increment. The occurrence of such obvious tachycardia precluded the use of a double blind protocol. This tachycardia was associated with palpitations in four subjects. At 15 min the palpitations were no longer present and mean heart rate rise was only 6.8 beats/min, but the bronchodilator effect, although less, was still highly significant.

With further increments there were small further increases in spirometric measurements but these were not significantly greater than the effects of the 150 μ g increment (cumulative dose 300 μ g). The highest mean 1 min heart rate rise was seen at an increment of 250 μ g (cumulative dose 750 μ g) and was 37 beats/min, falling to an acceptable level of 14 beats/min at 15 minutes. In one patient the heart rate rose by 90 beats/min 1 min after the 250 μ g increment. Gibson & Coltart (1971) suggested that the tachycardia seen with infusion of i.v. salbutamol is secondary to its peripheral β_2 vasodilator effect rather than to direct β_1 cardiac stimulation. The speed of onset of tachycardia and its association with marked palpitations make us suspect that the large rises seen within 1 min of bolus injection are in part at least due to direct β_1 cardiac stimulation. In addition there are marked and significant differences between the heart rate 1 min and 15 min after bolus injection. If diastolic blood pressure is accepted as a crude index of peripheral vasodilatation, then if the tachycardia was entirely secondary to peripheral vasodilatation it would be expected that diastolic blood pressure would be different at 1 and 15 min after injection, but there was no significant difference between this measurement at 1 and 15 minutes. We feel therefore that at 1 min the rise in heart rate is

partly due to direct β_1 stimulation and that this is due to the extremely high blood levels occurring after i.v. injection.

It should be remembered that the effect on heart rate may well depend on the state of the patient at the time of salbutamol injection. The patients in the present study were all convalescent and fit enough to show adequate response from inhalation of salbutamol aerosol. No patient had a resting heart rate greater than 90 beats/minute. In severe asthma, the pulse rate may be markedly elevated to values over 120 beats/minute. In such a situation the net effect of salbutamol *could be* to lower heart rate as the acute asthma attack is relieved.

Fitchett, McNicol & Riordan (1975), from dose-response studies in two patients with severe asthma, have shown an optimal effect from salbutamol (300 μ g) given intravenously over periods up to 1 minute. This is similar to our results from convalescent patients and shows that our data can be extrapolated for use in status asthmaticus.

The present study has shown that the major bronchodilator effect using the dose-response technique occurs after an incremental dose of 150 μ g, that is 300 μ g given as three doses over 45 minutes. We would suggest from a consideration of this data that in the treatment of an acute attack of asthma the initial i.v. bolus should be 250 μ g. This should be injected over a period greater than 1 min (2-5 min) and may be repeated if required after a 15 min interval. In hospital this may be combined with the commencement of an i.v. infusion of salbutamol as this often takes half an hour to have a marked effect (May, Spiro, Johnson & Paterson, 1975).

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