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INTRAVENOUS INFUSION OF SALBUTAMOL IN THE TREATMENT OF ASTHMA

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1 The effects of i.v. infusion of increasing rates of salbutamol for up to 4 h were documented in ten convalescent asthmatic patients.

2 The major bronchodilator effect was seen at 4.16 μg/minute. A small further improvement occurred at infusion rates up to 25.0 μg/min but was not significantly better than that seen at the lower infusion rate.

3 Cardiovascular effects were minimal after 60 min at the lower rate and even at 25.0 μg/min mean heart rate rose by only 17.1 beats/minute. All patients tolerated the 4 h infusion well.

4 It is concluded that i.v. infusion of salbutamol may be a useful addition to the treatment of the patient with a severe attack of asthma.

Introduction

Salbutamol (2-tertiary-butylamino-1- [4-hydroxy-3-hydroxymethyl] phenylethanol) is a β_2 adrenergic receptor stimulant widely used in the treatment of reversible airways obstruction. The effects of administration by the oral and inhaled routes have been well documented (Tattersfield & McNicol, 1969; Choo-Kang, Parker & Grant, 1970; Kamburoff & Prime, 1970; Walker, Evans, Richards & Paterson, 1972). During an attack of asthma, drug absorption following oral administration may be unreliable, and it may not be possible for the patient to inhale an aerosol preparation effectively. In this situation i.v. administration of bronchodilator drugs may be necessary.

The available data on i.v. infusion of salbutamol in patients with reversible airways obstruction has been obtained from studies in which the infusion was given for only a few minutes (Warrell, Robertson, Newton Howes, Conolly, Paterson, Beilin & Dollery, 1970; Paterson, Courtenay Evans & Prime, 1971; Svedmyr & Thiringer, 1971). In clinical practice i.v. infusion of bronchodilator may often have to be prolonged, and there is no information about the respiratory and circulatory effects, or the optimal infusion rate of salbutamol in such situations. We have studied the effects of salbutamol infusion in convalescent asthmatic patients to obtain this information.

Methods

Ten patients were studied (Table 1). All were convalescent asthmatics and had been shown previously to respond to the inhalation of salbutamol by an increase in forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and peak expiratory flow rate (PEFR), of at least 20%. In addition to asthma, one patient had chronic bronchitis, and one bronchiectasis. Patients over the age of 60 years, or with any evidence of heart disease were excluded. The consent of each patient was obtained after the procedures to be carried out had been fully explained. All patients were being treated with various bronchodilator drugs which were stopped the evening before the study. Corticosteroids and disodium cromoglycate were continued.

The patients were studied reclining on a couch. FEV_1 and FVC were measured using a dry spirometer (Vitalograph), and PEFR with a Wright's peak flow meter. Blood pressure was measured by conventional sphygmomanometry. The electrocardiogram was monitored continuously during the study on a cathode ray oscilloscope. In addition, a 12-lead electrocardiogram was performed before and after each study. Infusions were given via a cannula in a vein on the dorsum of the hand, controlled by a constant infusion pump (Palmer, infusion rates 0.08, 0.17,

Table 1 Summary of patients studied

				Pulmonary function tests (ATPS)					
				Predicted			Baseline before infusion		
Patient	*Age (years) sex*	*Weight (kg)*	*Diagnosis*	*FEV_1 (litres)*	*FVC (litres)*	*PEFR (litres/min)*	*FEV_1 (litres)*	*FVC (litres)*	*PEFR (litres/min)*
1	31 M	76.5	Asthma	3.65	4.35	615	1.45	2.85	270
2	41 F	57.2	Asthma	2.5	3.0	465	1.4	3.45	220
3	21 F	55.3	Asthma Bronchiectasis	3.0	3.5	515	2.15	2.15	395
4	40 M	85.7	Asthma	3.9	4.65	620	2.35	3.0	275
5	58 F	73.0	Asthma	2.4	3.1	430	1.0	1.5	220
6	45 M	62.5	Asthma	3.65	4.55	595	2.35	3.8	375
7	54 F	55.5	Asthma	2.0	2.55	430	0.7	1.5	100
8	32 M	59.4	Asthma Chronic bronchitis	4.15	4.9	630	1.2	3.6	150
9	58 F	59.5	Asthma	2.1	2.7	420	0.95	3.25	160
10	42 F	59.5	Asthma	2.2	2.7	455	1.7	2.6	185

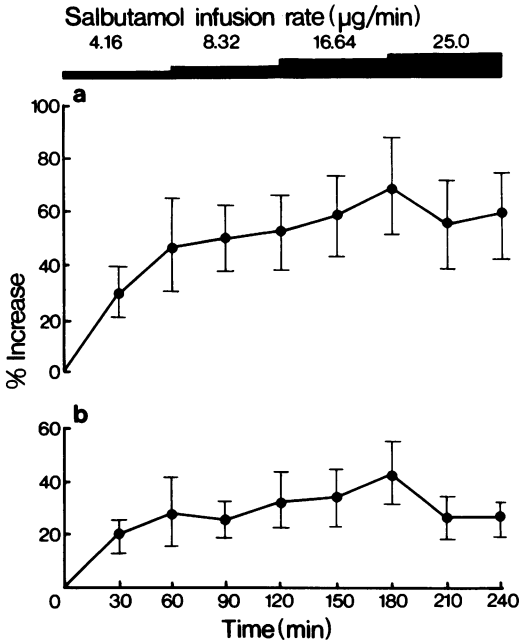

Figure 1 Effect (mean ± s.e. mean, n = 10) of salbutamol infusion on FEV_1 (a) and FVC (b).

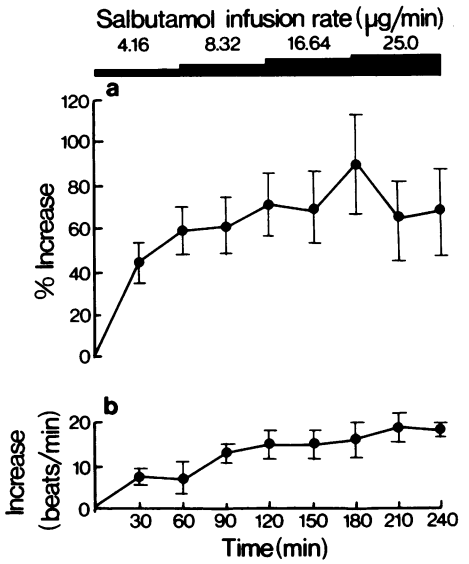

Figure 2 Effect (mean ± s.e. mean, n = 10) of salbutamol infusion on PEFR (a) and heart rate (b).

0.33 and 0.5 ml/min). Salbutamol was diluted in normal saline to a concentration of 50 μg/ml.

When steady baseline readings of FEV_1, FVC, PEFR, heart rate and blood pressure were obtained, salbutamol was infused at a rate of 0.08 ml/min ≡ 4.16 μg/minute. Every 60 min, the infusion rate was increased resulting in rates of 0.17 ml/min (8.32 μg/min), 0.33 ml/min (16.64 μg/min), and 0.5 ml/min (25.0 μg/min). Preliminary studies had suggested that infusions of 1-2 μg/min were relatively ineffective. Each patient received salbutamol for a total of 4 h, and physiological data were recorded every 15 minutes. The differences between mean values were analysed using Student's paired t test.

Results

All patients completed the study. Table 2 summarizes the observations made, expressed as mean (± s.e. mean) after 30 and 60 min at each infusion rate of salbutamol. The increase in FEV_1, FVC and PEFR was expressed for each patient as a percentage of the baseline value obtained before the beginning of the infusion. Change in heart rate, systolic and diastolic blood pressure was expressed as an absolute change from baseline values. This data is expressed graphically in Figures 1, 2 and 3.

Table 2 Physiological data during salbutamol infusions: mean (± 1 s.e. mean, n = 10)

Infusion rate (μg/min)	*Time (min)*	*Heart rate increase (beats/min)*	*Change in systolic BP (mmHg)*	*Change in diastolic BP (mmHg)*	*% Increase FEV_1 above baseline*	*% Increase FVC above baseline*	*% Increase PEFR above baseline*
4.16	30	6.7(2.0)	−5.0(3.7)	− 2.8(2.2)	30.4(9.3)	19.6(6.3)	43.2(9.2)
	60	6.6(3.9)	+2.0(6.2)	− 5.0(2.7)	47.8(17.6)	28.6(12.6)	57.6(11.5)
8.32	30	12.0(2.1)	−5.5(4.0)	− 7.5(2.1)	50.1(12.6)	25.1(7.8)	59.8(13.6)
	60	14.0(3.3)	−1.3(4.0)	− 7.5(3.4)	53.1(14.0)	32.7(10.0)	69.7(14.8)
16.64	30	14.2(3.3)	−3.3(4.0)	−10.0(2.6)	58.4(15.0)	33.1(10.9)	68.0(17.0)
	60	15.1(3.8)	−5.7(4.7)	−12.8(2.4)	69.4(18.6)	42.0(12.5)	87.8(23.6)
25.0	30	18.0(3.3)	−1.9(4.0)	−16.9(3.5)	55.6(17.0)	25.8(8.1)	61.0(18.8)
	60	17.3(1.3)	−3.8(4.7)	−15.6(4.4)	57.8(16.4)	26.1(6.8)	65.3(20.2)

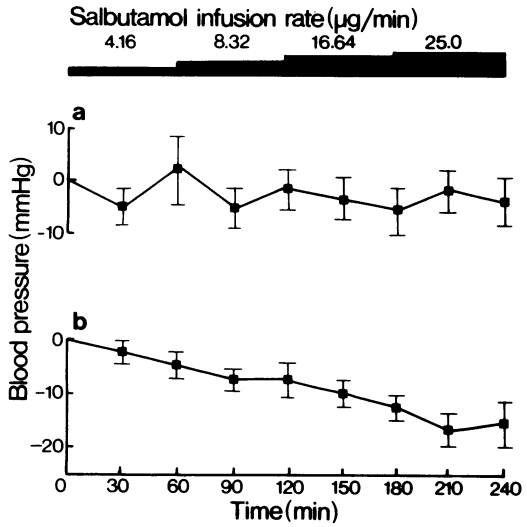

Figure 3 Effect (mean ± s.e. mean, n = 10) of salbutamol infusion on systolic (a) and diastolic (b) blood pressure.

Spirometry

The mean PEFR rose by 43% after 30 min and by 58% after 60 min at an infusion rate of 4.16 μg/minute. Both these rises were statistically significant ($P < 0.01$ and < 0.001 respectively). Although there was some further increase in PEFR, the values obtained after 60 min at infusion rates of 8.32, 16.64, and 25.0 μg/min were not significantly better than those obtained after 60 min at 4.16 μg/minute. Mean FEV_1 rose by 30% after 30 min and by 48% after 60 min at an infusion rate of 4.16 μg/minute. These rises were again significant ($P < 0.05$) but the small additional rises seen at higher infusion rates were not significantly better than the rise produced by 4.16 μg/minute. The mean percentage rise in FVC at an infusion rate of 4.16 μg/min was less than the rise seen in FEV_1 and PEFR at that rate, but was still statistically significant ($P < 0.02$).

Table 3 shows that the PEFR readings recorded during the infusion were comparable with the best PEFR previously recorded for the individual patient.

Heart rate and blood pressure

Table 2 and Figures 2 and 3 show the heart rate, systolic and diastolic blood pressure at each infusion rate. The mean heart rate increase was 6.6 beats/min after 60 min at an infusion rate of 4.16 μg/min, 14.0 beats/min at 8.32 μg/min, 15.1 beats/min at 16.64 μg/min, and 17.3 beats/min at 25.0 μg/minute. Compared with the baseline value, the increase at each of these infusion rates was statistically significant ($P < 0.02$). There was no significant difference in mean heart rate increase between infusion rates of 4.16 μg/min and 8.32 μg/min but the mean heart rate increases at 16.64 μg/min and 25.0 μg/min were significantly greater than that at 4.16 μg/min ($P < 0.05$). There was no statistical difference between the mean heart rate increases at 30 and 60 min at each infusion rate.

Systolic blood pressure did not change significantly at any infusion rate. However there was a progressive fall in average values of diastolic blood pressure with increasing infusion rates (Figure 3). This did not become significant until an infusion rate of 16.64 μg/min was reached ($P < 0.01$).

The greatest overall rise in heart rate seen in any patient during the study was 36 beats/min, and the greatest fall in diastolic blood pressure was 35 mmHg.

The electrocardiogram remained normal during and after the study. After cessation of the infusions, there was no evidence of sudden deterioration in respiratory function in any patient.

Muscle tremor was noted in some patients, particularly at higher infusion rates. However, in no patient were any of these effects sufficient to warrant discontinuation of the infusion.

Table 3 Comparison of highest PEFR previously recorded with highest PEFR during salbutamol infusion for each patient (litres/min)

	Patient									
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Highest PEFR previously recorded (litres/min)	440	355	465	485	440	385	280	380	315	285
Highest PEFR during salbutamol infusion (litres/min)	440	360	430	485	320	440	280	400	270	420

Discussion

Previous studies with i.v. salbutamol have shown that it is as effective as intravenous isoprenaline as a bronchodilator, but is 7-10 times less potent in increasing heart rate (Warrell *et al.*, 1970; Paterson *et al.*, 1971; Svedmyr & Thiringer, 1971; Gibson & Coltart, 1971). These studies were all done using short infusions of salbutamol, none being of more than 7 min duration. The present study assessed the effect of prolonged infusion of salbutamol as this is how the drug is used clinically. The greater part of the bronchodilatation achieved was obtained after 60 min at an infusion rate of 4.16 μg/min, with only a small increment being gained at higher rates, or longer durations of infusion (Figures 1 and 2). Marlin (1975) has reported the effect of low infusion of salbutamol in asthmatics and found effects in the same dose range.

The elimination half-life of i.v. salbutamol varies from 3-8 h in different subjects (Evans, M.E., personal communication). According to the plateau principle for i.v. infusions, the half-time for the shift from one steady state to another is identical to the half-time for elimination of the drug, and is not affected by the rate of infusion (Goldstein, Aronow & Kalman, 1974). Using this principle for salbutamol, the time to reach steady state plasma levels should be in the range of 6-16 hours. This is similar to data obtained for aminophylline by Mitenko & Ogilvie (1972).

However, the greater part of the clinical effect is achieved within 0.5-1 h and this is of considerable value. Because of this an initial i.v. bolus may be required in the treatment of an acute attack of asthma and this could be given at the same time as an infusion is commenced. Further work is in progress to investigate such a regimen in the management of acute asthma.

There was no significant difference in the mean increase in heart rate between infusion rates of 4.16 μg/min (6.6 beats/min) and 8.32 beats/min) and 8.32 μg/min (14.0 beats/min). As the major bronchodilator effect occurred at an infusion rate of 4.16 μg/min and little effect was seen at 1-2 μg/min, it would seem reasonable to start treatment at a rate of 4-5 μg/min and increase this to 8-10 μg/min if no response is seen after 30 minutes. Although the heart rate rises at 16.64 μg/min (15.1 beats/min) and 25.0 μg/min (17.3 beats/min) were significantly higher than those at lower rates they do not contra-indicate infusion of these higher rates if no bronchodilator effect were obtained at 4-10 μg/minute. Indeed other workers give much higher infusion rates in the treatment of premature labour. Liggins & Vaughan (1973) gave 43 μg/min intravenously to seventy-two patients. All experienced tachycardia, and in eleven (15%) heart rate rose to 140 beats/min and infusion was stopped without ill effect. Ng & Sen (1974) have used infusions of 33-133 μg/min and in only three patients systolic blood pressure fell by 30 mmHg. Although the clinical situation in these studies is different, there does seem to be a wide margin of safety as regards cardiovascular effects in the use of i.v. infusion of salbutamol.

Rebound bronchoconstriction has been described in occasional patients after inhaled isoprenaline (Keighley, 1966; Van Metre, 1969) and i.v. isoprenaline (Paterson *et al.*, 1971). In these patients a normal bronchodilator response was followed by severe bronchoconstriction. A suggested mechanism is that following a period of β stimulation the β adrenoceptors become refractory to stimulation and thus unresponsive to endogenous and exogenous sympathetic stimulation (Atkinson & Rand, 1968; Conolly, Davies, Dollery & George, 1971). In normal human subjects the dose of isoprenaline by bolus injection to produce tachycardia was increased following an i.v. infusion of isoprenaline (Conolly *et al.*, 1971). This could not be confirmed by Kingsley, Littlejohns & Prichard (1972).

None of our patients showed any 'rebound' deterioration during or following salbutamol infusion for 4 h, and Marlin (1975) found no resistance after infusion for 1 hour. Sims (1974) and Svedmyr (1973) were unable to demonstrate tolerance to the bronchodilator effects of β stimulation after chronic oral administration of either salbutamol or terbutaline.

In the management of acute asthma we would recommend initial infusion at a rate of approximately 5 μg/min which can be achieved by dissolving 5 mg in 500 ml of i.v. fluid giving a concentration of 10 μg/ml and infusion at 0.5 ml (approximately 8 drops)/minute. If no response is seen after 30 min, then the rate of infusion can be doubled to 1.0 ml/min (= 10 μg/min).

We are grateful to the physicians of the Brompton Hospital for allowing us to study patients under their care, and also to the staff of Blunt Ward for their help and co-operation. Allen & Hanburys Research Ltd, supplied the i.v. salbutamol. Mrs D. Denton typed the manuscript.

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References

ATKINSON, J.M. & RAND, M.J. (1968). Mutual suppression of cardiovascular effects of some beta-adrenoreceptor agonists in the cat. *J. Pharm. Pharmac.*, **20**, 916-922.

CHOO-KANG, Y.F.J., PARKER, S.S. & GRANT, I.W.B. (1970). Response of asthmatics to isoprenaline and salbutamol aerosols administered by intermittent positive-pressure ventilation. *Br. med. J.*, **4**, 465-468.

CONOLLY, M.E., DAVIES, D.S., DOLLERY, C.T. & GEORGE, C.F. (1971). Resistance to beta-adrenoceptor stimulants (a possible explanation for the rise in asthma deaths). *Br. J. Pharmac.*, **43**, 389-402.

GIBSON, D.G. & COLTART, D.J. (1971). Haemodynamic effects of intravenous salbutamol in patients with mitral valve disease-comparison with isoprenaline and atropine. *Postgrad. med. J.*, **47**, suppl. 5, 40-44.

GOLDSTEIN, A., ARONOW, Z. & KALMAN, S.M. (1974). The time course of drug action. In *Principles of Drug Action: The Basis of Pharmacology*. p. 312. New York & Toronto: John Wiley & Sons, Inc.

KAMBUROFF, P.L. & PRIME, F.J. (1970). Oral and inhaled salbutamol as a bronchodilator. *Br. J. Dis. Chest*, **64**, 46-54.

KEIGHLEY, J.F. (1966). Iatrogenic asthma associated with adrenergic aerosols. *Ann. intern. Med.*, **65**, 985-995.

KINGSLEY, P.J., LITTLEJOHNS, D.W. & PRICHARD, B.N.C. (1972). Isoprenaline-induced tachycardia in man. *Br. J. Pharmac.*, **46**, 539*P*-540*P*.

LIGGINS, G.C. & VAUGHAN, G.S. (1973). Intravenous infusion of salbutamol in the management of premature labour. *J. Obstet. Gynaec. Br. Commonw.*, **80**, 29-33.

MARLIN, G.E. (1975). Intravenous infusions of β_2-adrenoceptor agonists in the treatment of asthma. *Br. J. clin. Pharmac.*, **2**, 181-182P.

MITENKO, P.A. & OGILVIE, R.I. (1972). Rapidly achieved plasma concentration plateaus, with observations on theophylline kinetics. *Clin. Pharmac. Ther.*, **13**, 329-335.

NG, K.H. & SEN, D.K. (1974). Hypotension with intravenous salbutamol in premature labour. *Br. med. J.*, **3**, 257.

PATERSON, J.W., COURTENAY EVANS, R.J. & PRIME, F.J. (1971). Selectivity of bronchodilator action of salbutamol in asthmatic patients. Br. J. Dis. Chest, 65, 21-38.

SIMS, B.A. (1974). Investigation of salbutamol tolerance. *Br. J. clin. Pharmac.*, **1**, 291-294.

SVEDMYR, N. (1973). Proceedings of the Asthma Research Council Symposium on Evaluation of Bronchodilator Drugs. Trust for Education and Research in Therapeutics. In press.

SVEDMYR, N. & THIRINGER, G. (1971). The effects of salbutamol and isoprenaline on beta-receptors in patients with chronic obstructive lung disease. *Postgrad. med. J.*, **47**, suppl. 5, 44-46.

TATTERSFIELD, A.E. & McNICOL, M.W. (1969). Salbutamol and isoproterenol. A double blind trial to compare bronchodilator and cardiovascular activity. *New Engl. J. Med.*, **281**, 1323-1326.

VAN METRE, T.E. (1969). Adverse effects of inhalation of excessive amounts of nebulized isoproterenol in status asthmaticus. *J. Allergy*, **43**, 101-113.

WALKER, S.R., EVANS, M.E., RICHARDS, A.J. & PATERSON, J.W. (1972). The clinical pharmacology of oral and inhaled salbutamol. *Clin. Pharmac. Ther.*, **13**, 861-867.

WARRELL, D.A., ROBERTSON, D.G., NEWTON HOWES, J., CONOLLY, M.E., PATERSON, J.W., BEILIN, L.J. & DOLLERY, C.T. (1970). Comparison of cardiorespiratory effects of isoprenaline and salbutamol in patients with bronchial asthma. *Br. med. J.*, **1**, 65-70.

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