DETERMINATION OF THE OPTIMUM DOSE OF SUBCUTANEOUS SALBUTAMOL IN ASTHMATIC PATIENTS

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- 1 Saline and salbutamol (250 μ g, 500 μ g, 750 μ g and 1000 μ g) injections were administered under double-blind conditions to seven chronic stable asthmatic patients.
- 2 The response on the respiratory system (FEV_1 , FVC) and cardiovascular system (pulse rate, blood pressure and ECG) was monitored for 3 hours.
- 3 Increasing the dose of salbutamol increased the peak and weighted average effects of FEV_1 and pulse rate.
- 4 The optimum dose, a titration of desired increases in FEV_1 and undesirable increases in pulse rate, is 500 μ g but doses up to 1000 μ g may be administered if necessary.

Introduction

Bronchodilators are administered orally and by aerosol in the management of asthma and given parenterally in the treatment of acute severe bronchospasm and status asthmaticus. The drug used most frequently by the subcutaneous route is adrenaline which should be administered with extreme caution to asthmatic patients with low arterial oxygen tensions and chronic asthmatic patients with a significant degree of emphysema and related heart disease (Goodman & Gilman, 1970). Choo-Kang, Simpson & Grant (1969) have shown that salbutamol is a selective β_2 -adrenergic receptor agonist when administered by pressurized aerosol and is free from serious side effects after oral administration (Parker, Choo-Kang, Cooper, Cameron & Grant, 1971). A formulation suitable for subcutaneous administration is now available and it was decided to determine the optimum dose of salbutamol administered by this route. Oral and parenteral administration of salbutamol allows access of the drug to receptors, other than the β_2 -adrenergic receptors in bronchial smooth muscle, which result in pharmacological side effects e.g. enhancement of physiological tremor, considered to be a direct effect of β_2 -stimulant drugs on β_2 -adrenoceptors in skeletal muscle (Bowman & Nott, 1969; Richens & Watson, 1973) and increase in heart rate due to the effect of β_2 -stimulant drugs on arterioles producing peripheral vasodilation (Gibson & Coltart, 1971). The optimum dose of subcutaneous salbutamol

would thus be a titration of desirable increases in respiratory function and undesirable pharmacological side effects.

Method

Seven asthmatic patients volunteered to take part in the study after the aim and procedure had been explained to them. All had histories of chronic asthma, were in a stable phase at the time of the study but with a known good response to bronchodilators. Details of the patients are shown in Table 1. Each patient attended the respiratory function unit on five occasions. Measurements of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were recorded as the best of three successive forced expiratory manoeuvres on a vitalograph. Heart rate was recorded manually over a 60 s period and blood pressure by means of a sphygmomanometer. An estimation of physiological tremor was noted by observing the fingertips of the outstretched hand. Tremor was recorded as absent (0), mild (+), moderate (++) or severe (+++). All parameters were recorded before and at 5 min, 10 min, 15 min, 30 min, 60 min, 120 min and 180 min after injection. An ECG recording was taken before and 10 min after injection. The doses of salbutamol administered subcutaneously were 250 μ g, 500 μ g, 750 μ g and 1000 μ g, all in 0.5 ml

Figure 1 Mean % change in FEV_1 after administration of salbutamol ($\circ$ 250 μ g; $\blacksquare$ 500 μ g; $\triangle$ 750 μ g; $\blacktriangle$ 1000 μ g) or saline ($\bullet$) by subcutaneous injection in seven asthmatic patients. The figures in brackets indicate the mean FEV_1 in litres before the respective injections.

Figure 2 Mean % change in FVC after administration of salbutamol ($\circ$ 250 μ g; $\blacksquare$ 500 μ g; $\triangle$ 750 μ g; $\blacktriangle$ 1000 μ g) or saline ($\bullet$) by subcutaneous injection in seven asthmatic patients. The figures in brackets indicate the mean FVC in litres before the respective injections.

volume and the dose increased only if there were no unacceptable side effects with the preceding dose. A saline control was included and administered according to a previously randomized order. The injections were given by a separate member of staff to enable the study to be carried out under double-blind conditions. The local ethical committee gave their approval before the study commenced.

Patients were told to discontinue any bronchodilator drug at least twelve hours before the baseline recordings. Antibiotics were allowed if necessary and steroid therapy continued at a maintenance dose level. Coffee, tea and smoking were avoided for the duration of the study.

Results

The mean FEV_1 and FVC measurements in seven patients at baseline and the percentage change at the specified time intervals after injections are shown in Figure 1 and Figure 2. Increases in mean FEV_1 and mean pulse rate occurred after all active doses and are shown in Figure 3. Blood pressure was not affected by saline or salbutamol injection. The data on FEV_1 and pulse rate were subjected to statistical analysis to determine if the baseline values affected the responses on the respiratory (FEV_1) or cardiovascular systems (pulse rate). The aspects determined were peak effects, i.e. the mean of the highest individual FEV_1 or pulse rates

Table 1 Details of patients studied

Number	Age (years)	Sex	Weight (kg)	FEV_1 (litres)		FVC (litres)		Type of Asthma
				Predicted	Observed	Predicted	Observed	
1	46	F	57	2.4	0.65	3.4	1.25	Intrinsic Asthma
2	53	F	67	2.3	0.95	3.5	2.10	Extrinsic Asthma
3	52	F	77	2.3	1.35	3.3	2.35	Intrinsic Asthma
4	54	F	49	2.1	0.70	3.2	2.35	Extrinsic Asthma
5	43	F	77	2.7	0.95	3.3	1.45	Chronic Asthma/ Rhinitis
6	56	F	65	2.0	0.65	2.9	2.00	Bronchitis
7	48	F	59	2.4	0.60	3.6	1.45	Extrinsic — late onset intrinsic asthma

Figure 3 Relationship between mean peak improvements and mean weighted average effects of FEV₁ (●) and pulse rate (○) to increasing dose levels of subcutaneous salbutamol and saline administered subcutaneously to seven asthmatic patients.

and the weighted average effect, i.e. total area under the curve divided by the time over which the response was monitored. There was a significant correlation between baseline and both peak and weighted average effect for FEV₁ and pulse rate. In order to nullify the effect of the varying baselines for both FEV₁ and pulse rates it is possible to adjust the responses obtained to changes in FEV₁ and pulse rate originating from a common baseline value—the arithmetical mean of the baseline value at each dose level. Figure 3 illustrates the effect of placebo and all dose levels of salbutamol on FEV₁ and pulse rate using these adjusted figures. Increasing the dose of salbutamol increased the peak and weighted average effects of both FEV₁ and pulse rate.

Enhancement of physiological tremor increased in intensity and duration as the dose of salbutamol increased. No patient complained spontaneously of tremor. There were no abnormal changes in ECG recordings 10 min after administration of placebo or any dose level of salbutamol. No

Figure 4 Confidence limits of desirable and undesirable responses to subcutaneous salbutamol (0-1000 µg). The upper line indicates the upper limit of pulse increase (peak) and the lower line indicates the lower limit of FEV₁ increase (area).

patient complained of pain on injection at any dose level. There were no local reactions at the site of injection.

Discussion

All doses of salbutamol administered by subcutaneous injection produced an increase in FEV₁ and FVC. Increases in FEV₁ were directly related to the dose and in theory the dose which provided the greatest improvement in FEV₁ should be the recommended dose. In this study salbutamol (1 mg) produced the greatest improvement in FEV₁ but limitations were imposed by the effect of salbutamol on the cardiovascular system and on skeletal muscle. Marlin & Turner (1975) demonstrated a lack of relationship between the subjective assessment of tremor in the outstretched hand and amplitude of tremor recorded using an accelerometer and frequency analysis. This absence in relationship and the fact that no patient complained of tremor in this study limited the statistical analysis to the relationship between desired increases in FEV₁ and undesirable increases in pulse rate. Data in terms of FEV₁ were calculated with respect to weighted average effect because the response to bronchodilator activity includes integral factors associated with onset of activity, the peak values obtained and the duration of response. The effect of salbutamol on pulse rates is transient and the limiting factor of this aspect is the magnitude of the increases. Data on pulse rates were thus calculated in terms of peak effect.

Figure 4 illustrates the lower 95% confidence limits of the weighted average increases in FEV₁

Table 2 Comparison of the response to single doses of salbutamol administered by aerosol (200 µg), orally (4 mg), by intramuscular (8 µg/kg) and subcutaneous (500 µg, 750 µg, 1000 µg) injection

Route	Dose of salbutamol	% improvement in FEV ₁ over baseline				Total effect (Area under curve %FEV ₁ v. time (min))
		After 5 min	At peak	Time to reach peak (min)	After 180 min	
Aerosol	200 µg	42	47	50	42	149.42
Oral	4 mg	1	30	120	28	73.70
Intramuscular	8 µg/kg	72	74	15	61	246.35
Subcutaneous	500 µg	18	32	30	11	72.20
	750 µg	30	40	30	25	116.85
	1000 µg	28	40	60	32	122.70

and the upper 95% confidence limits of peak pulse rate increases for any dose of salbutamol (0.1 mg) administered subcutaneously. From these calculations the administration of salbutamol (500 µg) by subcutaneous injection would be expected to increase the pulse rate by a maximum of 20% (probability = 95%). This would represent a mean peak pulse rate of 96 beats/min from a baseline mean of 83 beats/min and could well represent the upper limit of acceptability. A dose of 750 µg would be expected to produce a mean peak pulse rate of 103 beats/min from the same baseline. It could be argued that both this and the higher incidence and severity of tremor represent an incidence of side effects that are not acceptable. The optimum dose appears to be in the order of 500 µg but it may well be worth using larger doses if necessary. The effect of mean peak pulse rates after administration of 1 mg was moderate (83 > 107 beats/min) and none of the patients complained spontaneously of tremor or palpitations at this dose level.

The use of salbutamol by aerosol administration (Choo-Kang *et al.*, 1969) or by mouth (Cochrane, Clark & Hanan, 1973) in the

management of asthma is well established. Ingram, Gaddie, Skinner & Palmer (1975) studied the response to intramuscular salbutamol in asthmatic patients. This paper has documented the response after subcutaneous administration and Table 2 attempts to compare the profile from all four centres. The best aspect of response is always obtained after intramuscular salbutamol. Oral administration is characteristically slow in onset of activity and the aerosol response would not be expected in a clinical situation involving hypersecretion of mucus, hyperaemia of the bronchial mucosa and infection. Subcutaneous salbutamol (500 µg) provides adequate response within five minutes but takes up to thirty minutes to reach peak activity. Decreased onset of activity, greater peak activity and total effect is obtained after administration of higher doses.

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