A COMPARATIVE TRIAL OF THREE METERED BRONCHODILATOR AEROSOLS IN ASTHMA

By J. L. Da Costa and B. K. Goh

SYNOPSIS

A single-blind comparative trial of three metered bronchodilator aerosols, Alupent, Ventolin and Medihaler Isoforte was carried out in 12 asthmatic patients. Using the dosage delivered by 2 separate valve releases, Ventolin was found to have a greater bronchodilatory cumulative effect than either Alupent or Medihaler and a greater peak response than Alupent. The duration of action of Alupent and Ventolin was greater than that of Medihaler although the latter attained a more rapid peak response. It was, however, not possible to compare the effects of equipotential peak dosages of the 3 drugs and this could account for the smaller peak and cumulative effects of Alupent that were found in this trial.

Metered bronchodilator aerosols are now well established in the treatment of asthma. Their advantage lies in easy portability and in their ability to deliver controlled small doses of drugs which achieve rapid and effective bronchodilatation. However, there have been recent reports of sudden death in asthmatic patients after excessive use of aerosols containing isoprenaline, orciprenaline and adrenaline and it is possible that they may have been caused by sympathomimetic-induced cardiac arrhythmias occurring in anoxic patients (Greenberg and Pines, 1967; Speizer *et al*, 1968). A new preparation, salbutamol (Ventolin, Glaxo Ltd.) is claimed to selectively stimulate the β_2-adrenergic receptors in bronchial muscle without much stimulation of β_1 receptors in the myocardium. It was therefore thought useful to compare this preparation with two other commonly used commercial aerosols containing isoprenaline and orciprenaline as regards bronchodilator activity and side effects.

MATERIALS AND METHODS

Twelve asthmatic patients (five men and seven women) were investigated. Their mean age was 33·9 ± 7·3 years. All had recurrent attacks of airway obstruction with a measurable response to isoprenaline in earlier studies. The three preparations were given in random order on separate, and for the most part, consecutive days. Special care was taken to ensure that the basal forced expiratory volume in one second (FEV_1) of each patient varied as little as possible, as the extent of response depends, among other factors, on the degree of bronchospasm. Each daily trial was started at 9 a.m. to obviate the known diurnal fluctuations in airway resistance that occur (Lewinsohn, 1960). To ensure absence of residual bronchodilator activity patients abstained from bronchodilators during the preceding 10 hours. Six patients on steroid therapy took their usual dosage during the tests.

FEV_1 and forced vital capacity (FVC) were measured with the patients seated using a Godart 9-litre closed-circuit spirometer. Results of the lung function measurements were expressed as per cent of predicted normal, using the nomogram of Da Costa and Goh (1971) for the normal values. Measurements were recorded in litres B.T.P.S. at 10 and 5 minutes before, and at 5, 30, 60, 120, 180, 240, 300 and 360 minutes after inhalation of the aerosol. The pulse rate was also recorded at these times. The mean of the two pretreatment values was used as the basal figure. Any side effects occurring during the trial were noted. One of the authors (B.K.G.) administered the inhalations to all the patients. Discharges from two separate valve releases were used in every case with a 30-second interval between the releases.

The dosage of the aerosol-inhalation administered by two valve releases in each case was as follows:

Medihaler Isoforte (Riker) : Isoprenaline sulphate 1000 ug

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Alupent (Boehringer-Ingelheim)	: Orciprenaline sulphate 1500 ug
Ventolin (Glaxo)	: Salbutamol 200 ug

RESULTS

The results obtained are summarised in Figs. 1, 2 and 3. Following each drug there was a depression of pulse rate and an increase in dynamic lung volumes. At the dosages used, Medihaler-Isoforte, gave a more rapid and greater increase in FEV_t and FVC at 5 minutes than either Ventolin or Alupent. However, Ventolin had a more prolonged duration of action.

The effects of the 3 drugs used were compared in terms of three aspects of response namely, Maximum or Peak Effect, Cumulative Effect and Duration of Effect. The results of these comparisons are shown in Tables 1, 2 and 3.

Administration of all three drugs resulted in a depression of the pulse rate (Fig. 1), Alupent showing the biggest drop. Its cumulative effect was also significantly greater than Medihaler (Table 1). There were no other significant differences.

The mean basal value of FEV_1 for Medihaler was significantly higher than that observed for the other two aerosols (Table II). However, there was no evidence to show that any of the aspects of response were related to the basal value. Ventolin produced a significantly higher peak than Alupent, a greater cumulative effect than either Medihaler or Alupent and a longer duration of effect than Medihaler. There were no other significant differences.

Ventolin showed a significantly greater cumulative effect on the FVC than Alupent (Table III). No other differences were significant.

Three patients complained of palpitations after Medihaler. In two they occurred at 5 minutes and in one at 60 minutes after drug administration. The other 2 aerosols did not give rise to any side effects.

DISCUSSION

The ideal way to estimate drug effect would be by comparison with a placebo. However, it was decided not to use a placebo in this trial for ethical reasons. Personal experience and the experience of other workers (Mattila and Muittari, 1966) has shown that studies in asthmatic patients involving repeated dynamic ventilation tests can cause considerable distress to the patient often provoking an attack of bronchospasm especially when such tests are carried out without protection of a bronchodilator. Also, as isoprenaline has been established as a standard bronchodilator it would suffice if the other drugs in the trial were compared with it. However, it must be noted that this study was designed to compare the effects of 3 commercial metered aerosols. The doses used were those recommended by the manufacturers and normally used in the treatment of asthma. It was not intended to make a direct comparison between the active components present in the aerosols as it has been established that the peak response and duration of response is dose-dependent (Freedman *et al*, 1968). A direct comparison of their effects should therefore only be made after giving standardised or equipotential peak doses (Freedman and Hill, 1971).

The results of this study indicate that using 2 'puffs' of each aerosol, Ventolin is a rapid, effective and long acting bronchodilator. This confirms earlier reports of Choo Kang *et al*, (1969), Kennedy and Simpson (1969) and Riding *et al*, (1970). Its bronchodilator activity was greater than Alupent and Medihaler though Alupent equalled it in duration of effect. Medihaler had the most rapid peak response but had a shorter duration of effect and gave rise to cardiovascular side effects in some patients.

Freedman *et al*, (1968) showed that weight for weight orciprenaline (the active component of Alupent) has 41·5% the potency of isoprenaline (the active component of Medihaler). Thus in this trial the dosage of orciprenaline (Alupent) used was less than an equipotential peak dosage of either isoprenaline (Medihaler-Isoforte) or salbutamol (Ventolin). This could have accounted for the smaller cumulative effect of Alupent. In spite of this, however, its duration of effect proved to be as long as Ventolin and greater than that of Medihaler.

A comparative trial of equipotential peak dosages of orciprenaline, salbutamol and isoprenaline would be of interest for a valid comparison of the duration of action and side effects of these drugs would then be possible. This was not possible with the commercially packed preparations used in this trial due to the prefixed dosage delivered per valve release. A recent study in asthmatic patients (Dan ϕ, 1971) comparing the effects of 400 ug salbutamol and 3000 ug orciprenaline (double the dosages administered in this trial) has shown that both salbutamol and orciprenaline are effective bronchodilators with nearly identical qualities and having no cardiovascular side effects even at these higher dosages. It would thus appear that although 2 puffs of Medihaler would be the maximum single dose recommended, 3-4 puffs of Ventolin or

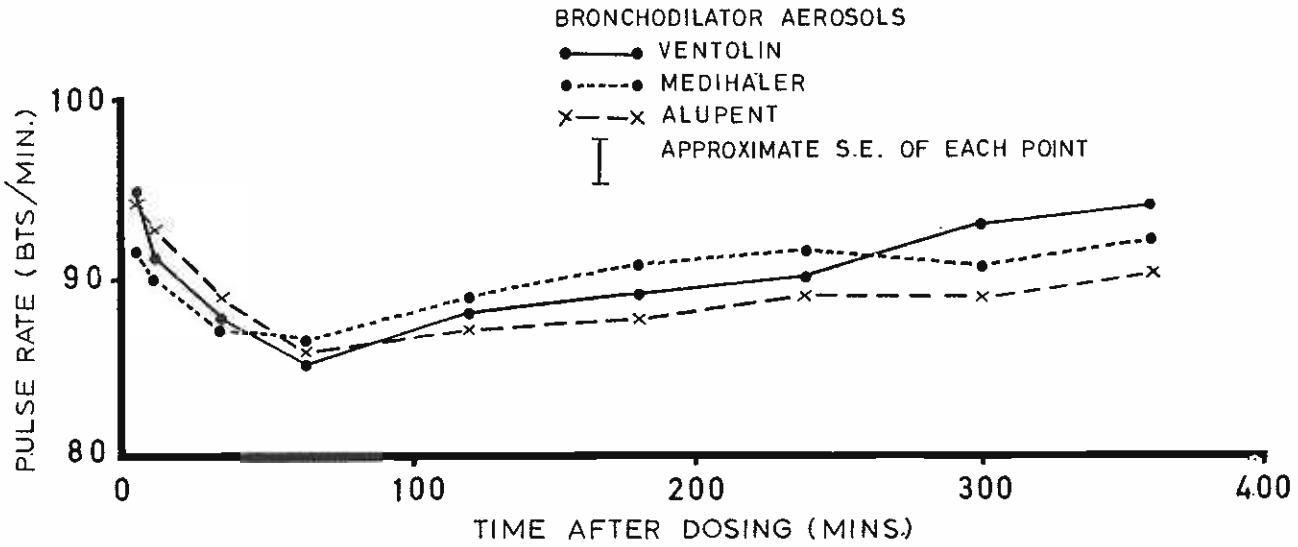

FIG. 1. Pulse rate after bronchodilator aerosols (means of 12 asthmatic patients)

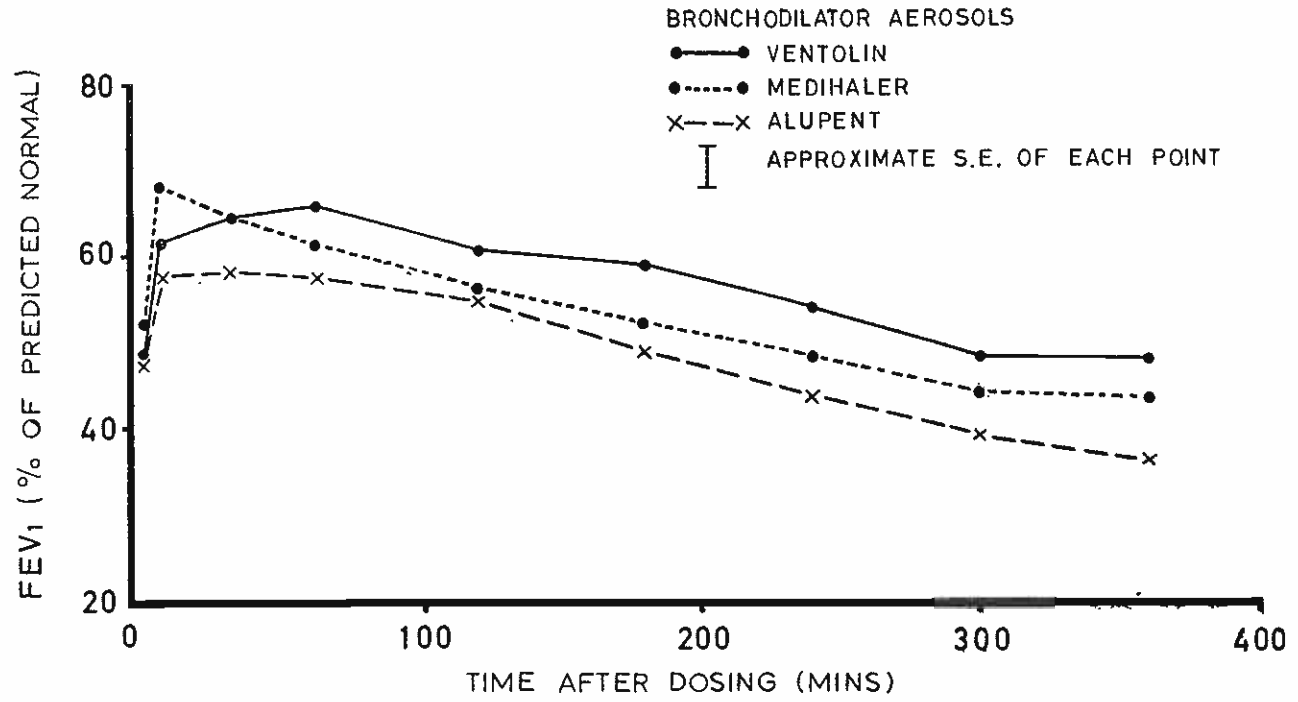

FIG. 2. FEV_1 after bronchodilator aerosols (means of 12 asthmatic patients)

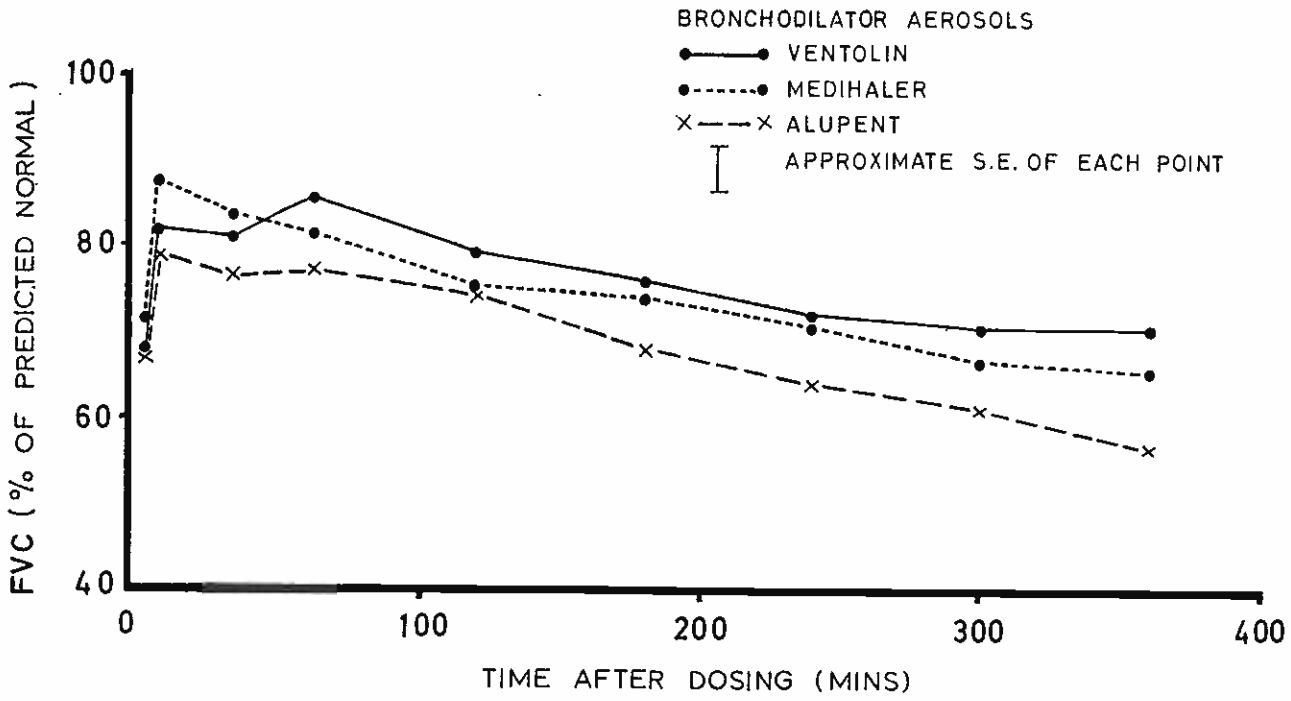

FIG. 3. FVC after bronchodilator aerosols (means of 12 asthmatic patients)

TABLE I

EFFECTS OF THE BRONCHODILATOR AEROSOLS ON THE PULSE RATE

Drug	Aspect of Response to Drug			
	Mean Basal Value	Mean Maximum Drop*	Mean Cumulative Effect** (Depression)	Mean Duration***
Ventolin	94·4 (a)	11·8 (a)	1699 (a) (b)	4·9 (a)
Medihaler	91·7 (a)	8·5 (a)	64 (a)	4·3 (a)
Alupent	94·1 (a)	11·9 (a)	2189 (b)	4·7 (a)
SE(M)	2·2	1·6	600	0·5
Critical Difference (p = ·05)	6·3	4·6	1756	1·5

* Maximum Effect = The largest drop in the pulse minus the basal value for each patient.

** Cumulative Effect = The area under the graph of result plotted against time minus the basal value times the length of study i.e. 6 hours.

*** Duration Effect = The time after which the measurements were not less than the basal value.

(a) (b): Any two treatment means having the same letter in common are not significantly different ($p > 0{\cdot}05$) using Student's t test.

TABLE II

EFFECTS OF THE BRONCHODILATOR AEROSOLS ON THE FEV_1 (% PREDICTED NORMAL)

Drug	Aspect of Response			
	Mean Basal Value	Mean Peak*	Mean Cumulative Effect**	Mean Duration***
Ventolin	48·5 (a)	21·1 (a)	3183 (a)	4·5 (a)
Medihaler	52·1 (b)	16·4 (a) (b)	345 (b)	3·1 (b)
Alupent	47·7 (a)	11·4 (b)	99 (b)	3·6 (a) (b)
SE(M)	1·2	1·9	888	0·5
Critical Difference ($p = ·05$)	3·3	5·4	2510	1·4

* Peak Effect = The largest effect minus the basal value for each patient.

** Cumulative Effect = The area under the graph of result plotted against time minus the basal value times the length of the study i.e. 6 hours.

*** Duration of Effect = The time after which the measurements were not more than the basal value.

(a) (b): Any two treatment means having the same letter in common are not significantly different ($p > 0·05$) using Student's t test.

TABLE III

EFFECTS OF THE BRONCHODILATOR AEROSOLS ON THE FVC (% OF PREDICTED NORMAL)

Drug	Aspects of Response to Drug			
	Mean Basal Value	Mean Peak*	Mean Cumulative Effect**	Mean Duration***
Ventolin	67·8 (a)	18·4 (a)	2947 (a)	4·5 (a)
Medihaler	70·8 (a)	17·8 (a)	1168 (a) (b)	3·9 (a)
Alupent	66·8 (a)	15·3 (a)	492 (b)	3·9 (a)
SE(M)	1·6	1·6	820	0·5
Critical Difference ($p = ·05$)	4·5	4·5	2300	1·5

* Peak Effect = The largest effect minus the basal value for each patient.

** Cumulative Effect = The area under the graph of result plotted against time minus the basal value times the length of the study i.e. 6 hours.

*** Duration of Effect = The time after which the measurements were not more than the basal value.

(a) (b): Any two treatment means having the same letter in common are not significantly different ($p > 0·05$) using Student's t test.

Alupent could be used at one time with greater bronchodilator effect and little danger of side effects.

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