COMPARATIVE EFFICACY OF SALBUTAMOL BY PRESSURIZED AEROSOL AND WET NEBULIZER IN ACUTE ASTHMA

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1 Cumulative dose-response curves (FEV_1) to pressurized aerosol salbutamol were established in 17 patients admitted to hospital with acute severe asthma. After the maximal pressurized aerosol effect had been achieved, a further dose (5 mg) of salbutamol was given by wet nebulizer and any further increment recorded.

2 Baseline FEV_1 was 1.16 ± 0.55 (mean $\pm$ s.d.), an average of 36% of predicted, and the maximal aerosol induced change in FEV_1 was 0.435 ± 0.330 l ($t=5.72$, $P<0.01$). There was an additional, small increment in FEV_1 after nebulizer of 0.043 ± 0.085 l ($t=2.26$, $P<0.05$).

3 Detailed analysis of the data according to a theoretical dose-response relationship showed that the nebulizer-aerosol increment was unrelated to asthma severity.

Introduction

There is still debate as to the most effective way of administering sympathomimetic bronchodilator drugs by aerosol in acute asthma (Leader, *Br. med. J.*, 1978); they may be inhaled either as an aerosol from a pressurized container ('dry aerosol') or from an aqueous solution via a wet nebulizer ('wet aerosol'). Pressurized aerosols are normally used in maintenance therapy and as the first treatment in acute attacks, whereas wet aerosols are often reserved for treatment of more severe attacks. Choo-Kang & Grant (1975) proposed that the more severe the asthma, the more effective is the wet aerosol compared to the pressurized form. The recommended dose of dry aerosol salbutamol in an acute attack and in maintenance treatment is 0.2 mg (2 puffs), although by wet aerosol the dose may be 5-10 mg. The difference in effective dosage is not as large as this, since it has been shown that only about 10% of a wet aerosol dose reaches the patient (Shenfield, Evans & Paterson, 1974). Even when this difference in availability is allowed for, an ideal assessment of the relative efficacy of the two methods would require construction of separate dose-response curves so that maximal effects could be compared. However, this is not possible in acutely ill patients and in the present study a cumulative dose-response curve for pressurized aerosol salbutamol was established in each patient, followed thereafter by a single large dose of wet aerosol; any additional increase (or decrease) in effect after the wet aerosol was taken as a measure of relative efficacy.

Methods

Seventeen patients with a mean age of 43 years (range 16-65) who were admitted to Fremantle Hospital, W.A. with acute asthma were studied within 24 h of admission. All gave informed consent to the study. Two patients were each studied on two separate occasions during different admissions for acute asthma, making a total of 19 studies. Recruitment was limited to those who were able to perform a forced expiratory manoeuvre. All patients were given standard treatment. This consisted of a bolus dose of intravenous hydrocortisone, and continuing therapy with high-dose oral prednisolone. No patient received intravenous aminophylline. The routine management included nebulized salbutamol at four-hourly intervals, but no patient received salbutamol or other sympathomimetic by either inhalation or injection, in the four hours prior to study.

Forced expiratory volume in one second (FEV_1) was measured with a Vitalograph spirometer and the mean of three readings was recorded. Following the baseline measurement, two puffs (0.2 mg) of pressurized aerosol (salbutamol) were inhaled under supervision and 15 min later, three FEV_1 readings were again recorded. This cycle of two puffs of salbutamol followed by FEV_1 measurement was repeated until serial pairs of readings were considered by the observer not to show any improvement which was clinically significant. This was established by visual inspection of the traces, and clinical observation of the patient. Salbutamol (5 mg) was then administered via a compressed air driven

nebulizer (Mini-neb, Inspiron) over 5–10 min, and the FEV₁ measured (three readings) 15 min after nebulization was finished.

Because of the possibility that the observer was mistaken in concluding that no further spirometric improvement was likely to occur, a further theoretical analysis of the data was performed. Cumulative dose-response curves for pressurized aerosol in each patient were constructed and fitted to a hyperbolic function (Equation 1) by non-linear least squares regression using all the recorded data (Metzler, 1969).

$$FEV_1 = FEV_{1, \text{base}} + \frac{\Delta FEV_{1, \text{max}} D}{D_{50\%} + D} \quad (1)$$

where FEV₁ = estimated FEV₁ according to the model, FEV_{1, base} = baseline FEV₁, FEV_{1, max} = maximal drug induced change in FEV₁, D = dose of dry aerosol salbutamol (in puffs), D_{50%} = salbutamol dose to give 50% of maximal response.

This equation is derived from a plot of all recorded points, beginning from FEV_{1, base} and incorporating the doses of dry aerosol salbutamol. The equation is used to estimate the maximal possible drug induced change in FEV₁ from pressurized aerosol salbutamol. This is a check as to whether the observer's judgement that maximal change had occurred, prior to administering wet aerosol salbutamol, was correct.

Incremental change in FEV₁ due to wet aerosol was taken as the difference between observed wet aerosol FEV₁ and the predicted dry aerosol FEV₁ if a further two puffs had been given. The ability of different factors to predict this increment was evaluated by multiple regression (Nie, Hull, Jenkins, Steinbrenner & Bent, 1975). In these regressions, the patient's best FEV₁ (FEV_{1, best}) was determined from spirometric records in the clinical case notes prior or subsequent to the admission during which the study was undertaken; predicted FEV₁ (FEV_{1, pred}) was calculated according to Cherniack and Raber (1972); asthma irreversibility as (FEV_{1, pred} - FEV_{1, best})/FEV_{1, pred}; asthma severity as FEV_{1, base}/FEV_{1, best}; and intrinsic and extrinsic asthmatics were classified according to Scadding (1977).

Results

Table 1 lists the basic attributes of the patients. There were eight female and two male intrinsic asthmatics with ages of 53 ± 9 years (mean ± s.d.), baseline FEV₁ of 0.94 ± 0.54 l and an average percentage of predicted FEV₁ of 34%. There were five male and two female extrinsic asthmatics with ages of 27 ± 14, baseline FEV₁ of 1.46 ± 0.44 l and an average percentage of predicted FEV₁ of 39%.

Table 2 shows the responses to pressurized and nebulized aerosol. The maximal increase in FEV₁ due to pressurized aerosol was 0.322 ± 0.154 l for the intrinsic asthmatic group and 0.591 ± 0.444 l for the extrinsic group and both these increases were significant at the 1% level. The number of puffs required to achieve this response was 6.95 ± 2.15, with no significant difference between the two groups. None of the patients showed harmful effects related to dry aerosol doses in excess of the recommended two puffs. There was a further increase in FEV₁ of 0.059 ± 0.059 l (*t* = 6.85, *P* < 0.01) for the extrinsic group following nebulizer (wet-dry increment), but no significant increase for the intrinsic group (0.031 ± 0.030 l, *t* = 1.03, *P* > 0.30).

Analysis of these data in terms of the theoretical dose response curve (Equation 1) made little difference. For the intrinsic group ΔFEV_{1, max} was 0.44 ± 0.20 l, D_{50%} was 4.5 ± 3.5 puffs and the wet-dry increment was 0.025 ± 0.084 l, while for the extrinsic asthmatics these figures were 0.66 ± 0.39 l, 1.8 ± 1.8 puffs and 0.067 ± 0.045 l respectively; the wet-dry increment was significant for the extrinsic group (*t* = 4.19, *P* < 0.01) but not for the intrinsic group. Since the wet-dry increment for the intrinsic asthmatics was not significantly different from zero it was not surprising to find that none of the considered predictors (age, sex, degree of asthma severity and irreversibility, FEV_{1, pred} and FEV_{1, best}) showed significant correlation. However, with the significant increment in the extrinsic group, a search for important clinical predictors revealed that 98% of variation in the wet-dry increment could be explained by D_{50%}, FEV_{1, best} and the degree of asthma irreversibility, the increment decreasing as each of these variables increased.

Discussion

In this study, three FEV₁ readings were obtained after each dose increment of dry aerosol, and also after the single dose of wet aerosol. There was no significant order effect in these readings, and furthermore the distribution of residuals about the mean of each set was not sufficiently asymmetric to use other than the mean. Ferris, Anderson & Zickmantel (1965) used mean readings in collating a normal series of FEV₁, but Fletcher, Peto, Tinker Speizer (1976) concluded in their long term study of 792 chronic bronchitics that maximal FEV₁ was preferable to mean FEV₁ because reproducibility was better. The standard deviation of maximal FEV₁ readings in their study was 3% less than that for mean FEV₁. In some patients with asthma, serial forced expirations show a progressive fall, because of the increasing severity of airflow obstruction which may occur as a result of the forced expiratory manoeuvre.

Table 1 Individual patient characteristics

<i>Asthma type</i>	<i>Patient</i>	<i>Sex</i>	<i>Age (years)</i>	<i>Baseline FEV₁ (l)</i>	<i>Best FEV₁ (FEV_{1,best}) (l)</i>	<i>Predicted FEV₁ (FEV_{1,pred})</i>	$\frac{100 \times FEV_{1,base}}{FEV_{1,pred}}$
Intrinsic	1	F	48	0.42	2.0	2.48	17
				1.2			48
	2	M	51	1.59	2.7	3.5	45
	3	F	61	0.81	1.3	2.55	32
	4	F	37	2.11	2.6	2.83	75
	5	F	59	0.39	1.5	2.29	17
	6	F	49	0.8	1.27	2.54	31
	7	F	59	0.42	1.2	2.62	16
	8	F	48	1.06	1.58	2.47	43
	9	F	65	0.54	0.99	2.59	21
	10	M	54	0.99	1.62	3.8	36
Mean $\pm$ s.d.			53 $\pm$ 9	0.94 $\pm$ 0.54	1.73 $\pm$ 0.58	2.74 $\pm$ 0.47	33.8 $\pm$ 17.9
Extrinsic	1	F	16	1.95	3.0	3.42	57
				1.31			38
	2	M	24	1.85	3.04	4.29	43
	3	M	17	1.95	3.3	4.47	44
	4	M	57	1.45	3.4	3.55	41
	5	F	36	0.82	1.5	2.91	28
	6	M	32	1.41	3.0	3.94	36
	7	M	21	0.92	2.8	4.02	23
Mean $\pm$ s.d.			27 $\pm$ 14	1.46 $\pm$ 0.44	2.88 $\pm$ 0.59	3.75 $\pm$ 0.52	38.7 $\pm$ 10.4
All Patients							
Mean $\pm$ s.d.			42 $\pm$ 7	1.16 $\pm$ 0.55	2.21 $\pm$ 0.81	3.1 $\pm$ 0.70	36 $\pm$ 15

FEV₁ given as the mean of three readings**Table 2** Observed FEV₁ response to pressurized and nebulized aerosol

<i>Asthma type</i>	<i>Patient</i>	<i>Maximal change, pressurized</i>	<i>Number of puffs</i>	<i>Further change in FEV₁ after nebulizer</i>
Intrinsic	1	0.17	8	-0.03
		0.34	8	0.24
	2	0.56	8	0.08
	3	0.16	6	0.17
	4	0.38	8	-0.07
	5	0.18	6	0.08
	6	0.35	8	-0.01
	7	0.08	6	-0.04
	8	0.44	6	-0.07
	9	0.38	6	-0.02
	10	0.50	6	0.01
Mean $\pm$ s.d.		0.322 $\pm$ 0.154	6.9 $\pm$ 1.0	0.031 $\pm$ 0.101
Extrinsic	1	0.52	6	0.15
		1.46	14	0.01
	2	0.66	4	0.07
	3	0.99	6	0.01
	4	0.17	6	0.12
	5	0.47	4	0.10
	6	0.27	8	0.01
	7	0.19	8	0.0
Mean $\pm$ s.d.		0.591 $\pm$ 0.444	7.0 $\pm$ 3.2	0.059 $\pm$ 0.059
All patients				
Mean $\pm$ s.d.	0.435 $\pm$ 0.330	6.95 $\pm$ 2.15	0.043 $\pm$ 0.085	

FEV₁ results given in litres

Following a bronchodilator, this progressive fall may be prevented although the 'best' FEV₁ is not greatly changed. Thus the mean rather than the 'best' FEV₁ may be a more appropriate measure of the efficacy of a bronchodilator (Asthma Research Council, 1974). For these reasons, and also because we wished to analyse the predicting factors for maximal FEV₁ response, we have used the mean of three FEV₁ readings.

The present study design did not include a complete dose-response curve for the wet aerosol. The difficulty in acute asthma is that treatment is ethically mandatory, and consequently a patient is not in a comparable clinical situation some hours after admission. It is possible that if a larger dose than 5 mg of wet aerosol had been given, the wet-dry increment in FEV₁ would have been greater. Ruffin, Obminski & Newhouse (1978) found no significant difference in FEV₁ response in nine asthmatic patients given wet aerosol salbutamol over the dose range 1, 2.5 and 5 mg measured 30 min to 4 h after administration, suggesting that the response to the 5 mg dose was maximal. The comparison between wet and dry aerosols was for different times after administration. For the pressurised aerosol given cumulatively over two to five 15 min intervals, there was a greater time for onset of drug action, whereas with wet aerosol only 15 min elapsed before the FEV₁ was recorded. The study by Webber, Shenfield & Paterson (1974) demonstrated that the peak effect after wet aerosol occurred at 10 min after the end of nebulization. Thus the 15 min reading used in the present study should fully reflect the maximal effect after wet aerosol.

It is difficult to relate this investigation to previous studies comparing wet and dry aerosols, either because there were often large differences in effective dose administered by the two routes (which would place responses on different parts of the dose-response curves) or because the patients were not suffering from acute asthma. Choo-Kang & Grant (1975) for example, studied convalescent patients and compared 10 mg by wet aerosol and intermittent positive pressure breathing, with 0.2 mg from a pressurized canister, so that the superiority of wet aerosol which they found could have been due to the relatively smaller pressurized aerosol dose. One comparable study (Cayton, Webber, Paterson & Clark, 1978) used 0.4 mg pressurized aerosol salbutamol and 5 mg wet aerosol in two groups of patients suffering from acute asthma. In the first group there was no further improvement with pressurized aerosol when given after the wet aerosol treatment. However, when given in reverse order to the second group, there was a further improvement in FEV₁ after wet aerosol, which was not statistically significant. Both this study and the present one therefore suggest that the average increase in efficacy

of wet as compared to dry aerosol in acute asthmatics, even if statistically significant, is small. For the clinician therefore, choice of inhalation mode may be a matter of convenience rather than of therapeutic policy. It is possible that for many patients, slow tidal volume breathing over 5–10 min with wet aerosol administration is a more convenient (although not inherently more effective) way of administering aerosol salbutamol in an effective dose as compared to sequential doses of dry aerosol every 15 minutes.

Interpretation of the multiple regression predictors of wet-dry increment in extrinsic asthmatics is made somewhat redundant by the small effect (0.059 ± 0.059 l), but nevertheless may be important given the high level of prediction found (98% of variation explained). The most important predictor was D_{50%}; as it increased the increment decreased, implying that an extrinsic asthmatic who responds poorly to sequential doses of dry aerosol salbutamol will not do any better with wet aerosol, and an alternative form of therapy may have to be considered. The important finding in these regressions was that for both intrinsic and extrinsic asthmatics, the efficacy of wet aerosol compared to dry aerosol was unrelated to severity.

The recommended pressurized aerosol salbutamol dose has been limited to two puffs (0.2 mg) partly because of concern that the increase in asthma deaths in the U.K. and some other countries was related to increased sales of sympathomimetic aerosol bronchodilators (Speizer, Doll, Heaf & Strang, 1968; Inman & Adelstein, 1969). Subsequent review of the evidence has suggested alternative possibilities for this correlation (Inman, 1974). A previous study of cumulative dose-response curves for isoprenaline (Cohen & Hale, 1965) suggested that 8–10 puffs might be necessary to provide maximal bronchodilatation and the results of this study suggest that 4–8 puffs of dry aerosol salbutamol may be needed. None of the patients in the present study experienced adverse effects at these higher dry aerosol doses.

In conclusion, our results do not show that wet aerosol salbutamol (5 mg) is clinically more effective than adequate doses of the dry aerosol form when given as a series of two puffs at intervals of 15 minutes. Although our studies were performed on patients who had acute severe asthma, patients who were unable to perform a forced expiratory manoeuvre were excluded. It may well be that such patients, who cannot perform an inspiratory vital capacity, may do comparatively less well with the pressurized aerosol and benefit from the wet aerosol. If clinically significant improvement with dry aerosol is going to occur (for example with extrinsic asthmatics), this improvement will occur after a relatively small number of puffs. We suggest

therefore that the choice of wet or dry aerosol salbutamol in the treatment of acute asthma, is a matter of convenience rather than of therapeutic policy. In certain circumstances it may be appropriate for patients with severe acute asthma to be instructed to take more than the recommended dose of pressurized aerosol salbutamol before admission to hospital. If there is no clinically significant improvement after either four to six puffs of dry aerosol, or 5 mg of wet aerosol salbutamol, then consideration should be given to additional forms of treatment, which may include parenteral

bronchodilators. This type of spirometric assessment after initial bronchodilator aerosol treatment of acute severe asthma may have a role in predicting the appropriate route (aerosol or parenteral) or nature of subsequent bronchodilator treatment.

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