Dose-response comparison of ipratropium bromide from a metered-dose inhaler and by jet nebulisation

SA GOMM, NP KEANEY, LP HUNT, SC ALLEN, TB STRETTON

From the Department of Respiratory Medicine, Manchester Royal Infirmary, Manchester

ABSTRACT The dose-response relationships of the anticholinergic bronchodilator drug ipratropium bromide were studied. Cumulative doses totalling 288 μg ipratropium were given by inhalation of a liquid aerosol from a Wright nebuliser to each of 10 patients with stable, moderately severe airflow obstruction. Up to 80% of the maximum achievable bronchodilator response, as assessed by a rise in the patients' mean forced expiratory volume in one second (FEV_1), was obtained with a cumulative total dose of 72 μg; with additional doses beyond 72 μg there was no significant further improvement. In the same patients the effects of administration of cumulative doses of ipratropium to a total of 72 μg from a Wright nebuliser were compared with those achieved with a metered-dose inhaler. Bronchodilatation was assessed by measurement of peak expiratory flow rate, FEV_1, forced vital capacity, thoracic gas volume and specific airways conductance (sGaw). No significant difference was observed in the response at any dose level between the wet and the dry aerosols. By fitting a curve to the mean values of FEV_1 and sGaw an estimate was made of the dose of ipratropium bromide required to produce 99% of the achievable bronchodilator response. For FEV_1 this dose was 78 μg when ipratropium was inhaled as a nebulised solution from the Wright nebuliser and 82 μg when it was inhaled from the metered-dose inhaler; for sGaw the respective values were 54 and 58 μg. In these patients with stable airflow obstruction there was no therapeutic advantage in the use of ipratropium bromide as a wet aerosol.

The inhalation of low doses of a bronchodilator drug from a pressurised metered-dose inhaler is standard practice in the maintenance treatment of reversible airflow obstruction. For acute exacerbations necessitating admission to hospital large doses of the bronchodilator are often administered by nebulisation of a solution of the drug, with or without the assistance of intermittent positive-pressure ventilation. Previous reports [1-3] of the superiority of liquid nebulisation over a metered-dose inhaler for administering β-adrenoceptor bronchodilator aerosols appear to overlook the discrepancy between the doses administered. We have made a comparative study of the bronchodilator effect of the anticholinergic drug ipratropium bromide given in equal, low doses by jet nebulisation and from a metered-dose inhaler. Ipratropium bromide is being used increasingly in the treatment of patients with airflow obstruction, a dose of 20–80 μg from a metered-dose inhaler producing a peak effect after 30–40 minutes and an action which may persist for up to six hours.[4-6] The objectives of the present study were twofold: firstly, to determine the dose of ipratropium given as a nebulised solution which was needed to produce a plateau in the magnitude of the resulting bronchodilatation and, secondly, to compare the dose-response relationships of administering equal doses of the drug from a Wright nebuliser and a metered-dose inhaler.

Methods

The study was performed on 10 patients aged 20–67 years, whose clinical details are summarised in table 1. Eight of the subjects had bronchial asthma and two chronic bronchitis; nine were non-smokers. Individuals were excluded if they had evidence of any other bronchopulmonary disease or disease in any other system. Each patient gave informed con-

Address for reprint requests: Dr SA Gomm, Department of Chest Medicine, Wythenshawe Hospital, Manchester M23 9LT.

Table 1 *Details of the patients in the study, with baseline forced expiratory volume in one second (FEV[1]) and improvement 15 minutes after inhalation of 200 µg salbutamol*

Patient	Sex	Age (y)	Duration of illness (y)	Diagnosis*	FEV[1]		
					Baseline		Improvement after salbutamol (l)
					l	% predicted[9]	
1	M	20	10	A	2·68	63	3·23
2	M	52	30	CB	0·96	29	1·19
3	F	39	36	A	1·17	46	1·80
4	M	47	34	A	1·38	40	1·66
5	F	60	14	A	0·94	43	1·27
6	M	63	10	CB	1·23	43	1·48
7	M	34	6	A	1·86	41	2·29
8	F	58	5	A	1·52	65	2·28
9	F	62	10	A	1·08	60	1·36
10	M	67	9	A	1·98	56	2·45

*A—asthma as defined by Ciba Foundation Study Group;[7] CB—chronic bronchitis as defined by Medical Research Council.[8]

sent to the study. All had a baseline forced expiratory volume in one second (FEV[1]) which was less than 70% of their predicted normal value[9] and an improvement in FEV[1] of more than 20% after inhaling 200 µg of salbutamol. In addition, their FEV[1] did not vary by more than 12½% between study days. Bronchodilator drugs were discontinued for the 12 hours preceding each experiment but patients receiving corticosteroids or disodium cromoglycate continued these drugs during the study. All the patients were experienced users of metered-dose inhalers.

Ipratropium bromide was supplied in two ways: *(a)* from a pressurised metered-dose inhaler, each activation delivering 18 µg to the patient, and *(b)* as a solution administered from a Wright nebuliser[10] in a dilution such that the required dose of ipratropium could be delivered during two minutes of nebulisation via an MC face mask at an oxygen flow rate of 6 litres a minute. Each patient was instructed to use tidal breathing when the solution of ipratropium was inhaled from the Wright nebuliser. In a series of 10 two-minute nebulisations it was shown by weighing the Wright nebuliser beforehand and afterwards that the mean volume of solution emitted was 440 µl ± 47 µl (SEM). A stock solution of ipratropium was prepared containing 144 µg/ml and aliquots of this were diluted in normal saline to deliver the desired dose on the assumption that 440 µl of diluted solution would be emitted. The same Wright nebuliser containing 5·0 ml of diluted solution was used throughout the study.

CUMULATIVE INHALATION STUDY USING JET NEBULISATION
The patients attended the laboratory at 9 am and rested for 20 minutes. Baseline values of PEFR, FEV[1] and FVC were measured on an Ohio 842 dry cylinder spirometer and the pulse rate was recorded.

Ipratropium bromide was administered from the Wright nebuliser through a face mask in doses of 18, 18, 36, 72 and 144 µg at 30-minute intervals. The physiological measurements were repeated before each succeeding dose of ipratropium and 30 minutes after the last dose.

DOSE-RESPONSE COMPARISON USING METERED-DOSE INHALER AND JET NEBULISATION
The patients attended the laboratory on two consecutive days. They rested for 20 minutes and control values of peak expiratory flow rate, FEV[1], forced vital capacity (FVC), thoracic gas volume (TGV), airways resistance (Raw), and pulse rate were recorded. Measurements of PEFR, FEV[1], and FVC were made with an Ohio 842 spirometer. A pressure-corrected flow plethysmograph (Fenyves and Gut) was used to measure TGV and Raw[11] and the results were expressed as the reciprocal of airways resistance per litre of thoracic gas volume—that is, specific airways conductance (sGaw).

On one treatment day each subject received ipratropium bromide from a metered-dose inhaler at 30-minute intervals in doses of 18, 18, and 36 µg. On the other treatment day ipratropium was inhaled through a face mask from the Wright nebuliser in doses of 9, 9, 18, and 36 µg at 30-minute intervals. The method of administration on the first treatment day was randomly allocated to each patient. The physiological measurements were repeated 30 minutes after each dose of ipratropium and at 30 and 60 minutes after the patient had received a cumulative dose of 72 µg. This was done for each method of administration of the drug. Dose-response curves were prepared and the results for the two methods of administration were compared. The significance of differences between the mean values were compared by paired *t* tests and a
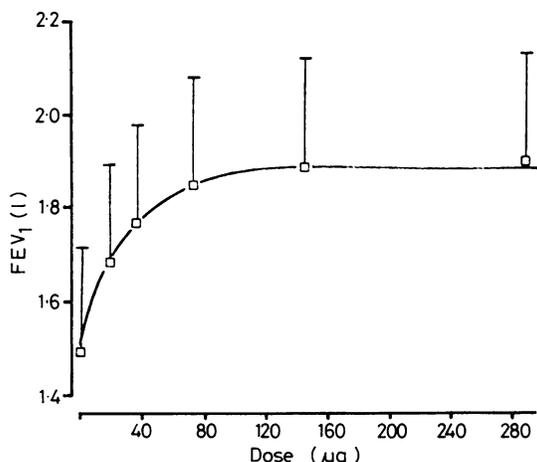
Fig 1 *Mean values (± SEM) of FEV₁ (l) after administration of ipratropium bromide from a Wright nebuliser to a cumulative dose of 288 µg in 10 patients, each value of FEV₁ after the first representing the value observed 30 minutes after inhalation of the indicated dose.*

multivariate equivalent using one-sample Hotelling's T².[12]

Results

CUMULATIVE INHALATION STUDY USING JET NEBULISATION
The mean control value for FEV₁ before the patients used the Wright nebuliser was 1·50 ± 0·22 litres. The maximum value obtained for FEV₁ was 1·92 ± 0·28 l; this occurred 30 minutes after the cumulative inhalation of 288 µg of ipratropium. The bronchodilatation at each dose level was highly significant (p < 0·001) (fig 1). The cumulative administration of 72 µg of ipratropium by jet nebulisation produced 80% of the maximum improvement in FEV₁ and there was no significant difference between the 72 µg and 288 µg dose levels.

DOSE-RESPONSE COMPARISON USING METERED-DOSE INHALER AND JET NEBULISATION
The mean baseline FEV₁ before the patients used the metered-dose inhaler was 1·49 ± 0·19 l and before jet nebulisation 1·52 ± 0·21 l. There was no significant difference in the mean maximum postbronchodilator values of FEV₁, which were 2·09 ± 0·28 l and 1·97 ± 0·27 l respectively. The cumulative administration of 72 µg of ipratropium bromide by both methods produced highly significant improvements (p < 0·001) in the mean values for PEFR, FEV₁, FVC, TGV, and sGaw at the cumulated 18 µg, 36 µg, and 72 µg dose levels and at 30 and 60 minutes after inhalation of 72 µg of ipratropium (table 2). The changes which occurred with each dose increment above the cumulated 18 µg level were not, however, significant. For all measured respiratory indices at each dose level there was no significant difference between the response to

Table 2 *Comparison in 10 patients with airflow obstruction of metered-dose inhaler (A) and Wright nebuliser (B): results of spirometry and whole-body plethysmography (means ± SEM)**

		Base-line	Cumulative dose ipratropium				Minutes after 72 µg dose level	
			9 µg	18 µg	36 µg	72 µg	30	60
FEV₁ (l)	A	1·49		1·88	2·00	2·06	2·00	2·02
		(0·19)		(0·23)	(0·27)	(0·29)	(0·27)	(0·27)
	B	1·52	1·71	1·86	1·90	1·96	1·89	1·74
		(0·21)	(0·22)	(0·25)	(0·25)	(0·26)	(0·23)	(0·23)
FVC (l)	A	2·63		3·10	3·25	3·28	3·42	3·36
		(0·31)		(0·34)	(0·33)	(0·35)	(0·33)	(0·30)
	B	2·66	2·87	3·10	3·22	3·11	3·15	3·03
		(0·32)	(0·34)	(0·35)	(0·36)	(0·37)	(0·30)	(0·30)
PEFR (1 min⁻¹)	A	209		259	285	293	272	275
		(29)		(37)	(43)	(44)	(40)	(39)
	B	208	236	266	273	266	259	234
		(29)	(29)	(32)	(36)	(40)	(32)	(34)
sGaw (s⁻¹ kPa⁻¹)	A	0·46		0·99	0·98	1·16	1·15	1·17
		(0·06)		(0·16)	(0·18)	(0·23)	(0·24)	(0·33)
	B	0·52	0·68	0·88	0·89	0·90	0·94	0·86
		(0·08)	(0·16)	(0·16)	(0·14)	(0·13)	(0·23)	(0·19)
TGV (l)	A	4·43		4·15	4·14	4·02	3·93	3·87
		(0·33)		(0·34)	(0·36)	(0·31)	(0·28)	(0·30)
	B	4·45	4·26	4·06	4·02	3·96	3·94	4·03
		(0·38)	(0·37)	(0·36)	(0·33)	(0·31)	(0·29)	(0·32)

FVC—forced vital capacity; PERF—peak expiratory flow rate; sGaw—specific conductance; TGV—thoracic gas volume.
*The mean improvement in FEV₁, FVC, PEFR, TGV, and sGaw compared to baseline values was significant (p < 0·001) at the cumulated 18, 36, and 72 µg dose levels and at 30 and 60 minutes. Improvement in FVC, TGV, and sGaw was not significant at the 9 µg dose (n = 10).

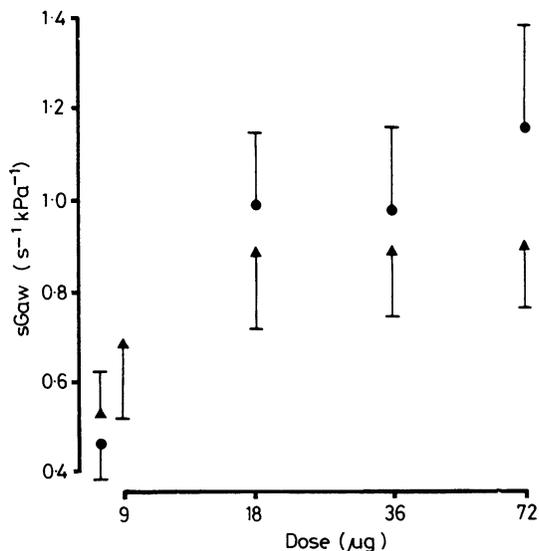Fig 2 *Mean values (± SEM) of sGaw (s⁻¹ kPa⁻¹) before and after administration of ipratropium bromide to a cumulative dose of 72 µg from a metered-dose inhaler (●) and a Wright nebuliser (▲) in 10 patients.*

Fig 3 *The exponential model $y = A - Be^{-Cx}$, to which the dose-response data were fitted. y = mean FEV_1 or sGaw (l); x = cumulative dose (µg) of ipratropium; A is the theoretical maximum bronchodilator response; B is the maximum increase in the mean values; A–B is the response before the drug was inhaled; and C is a constant of proportionality.*

recorded were 86 (±9·1) and 84 (±11·1) beats/min respectively.

Discussion

ipratropium bromide with the metered-dose inhaler and that achieved with the Wright nebuliser (table 2 and fig 2).

For each method of administration the bronchodilator effect of ipratropium as measured by the mean values of FEV_1 and sGaw appeared to be exponentially related to the dose of drug received and it fitted a curve of the form $y = A - Be^{-Cx}$ (fig 3). In the equation y is the mean value of FEV_1 or sGaw; x is the cumulative dose (µg) of ipratropium bromide; A is the theoretical maximum bronchodilator response; B is the maximum increase in the mean values of FEV_1 or sGaw; A–B is the response before ipratropium bromide was inhaled and C is a constant of proportionality. The constants A, B, and C were estimated by a method of iterative computer analysis.[13] The curve obtained for each response was plotted graphically and the actual data points for FEV_1 and sGaw were inserted for comparison. The dose of ipratropium bromide required to produce 99% of the theoretical maximum bronchodilator response was estimated from the dose-response curves. For FEV_1 this dose was 78 µg when the drug was inhaled as a nebulised solution from the Wright nebuliser and 82 µg when it was inhaled from the metered-dose inhaler; for sGaw the respective values were 54 and 58 µg.

The mean baseline value for pulse rate when the patients used the metered-dose inhaler was 82 beats per minute (± SD 8·2) and 81 beats/min (±10) when they used the nebuliser. The maximum values

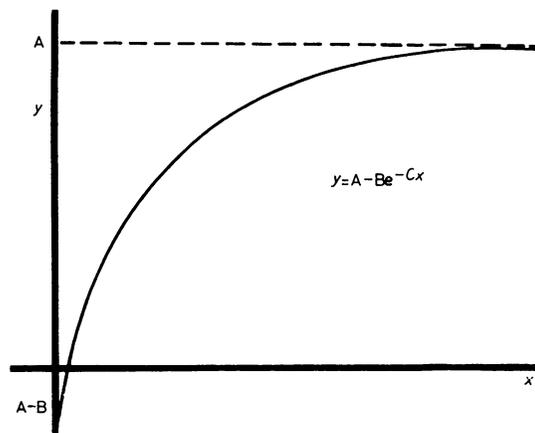The results of the initial study in this group of patients with moderately severe airflow obstruction showed that about 80% of the maximum bronchodilatation produced by ipratropium bromide could be achieved with a cumulative dose of 72 µg. When the effects of equivalent doses of the drug given by metered-dose inhaler and as a nebulised solution were then compared there was no evident difference in the degree of bronchodilatation achieved.

Important factors influencing aerosol penetration into the lungs include the size and distribution of the particles inhaled,[14] the technique of inhalation,[15-17] and abnormalities in the airway structure.[18] The diameter of particles delivered by a metered-dose inhaler is reported to be below 5 µm[19] and from a Wright nebuliser below 8 µm.[10] In the present study the techniques of inhalation of the bronchodilator under investigation were intentionally different but the degree of airflow obstruction in the participants was of comparable severity on the days when ipratropium was administered by the two methods.

Shenfield and coworkers[20] reported that less than 20% of the delivered dose of nebulised salbutamol enters the patient, the proportion reaching the lungs being uncertain; while 10% of the delivered dose from a metered-dose inhaler is estimated to enter the lungs.[21 22] Our findings of comparable bron-
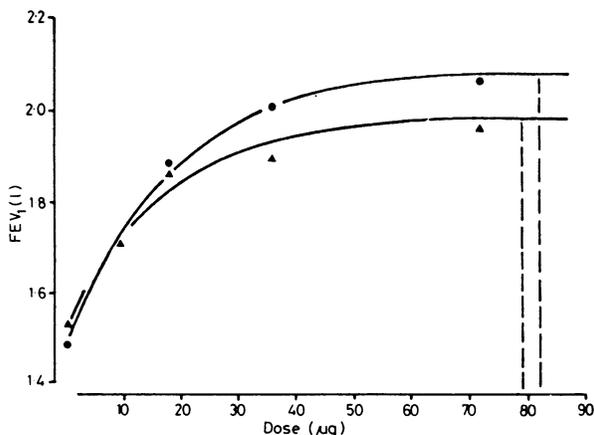
Fig 4 *The exponential model $y = A - Be^{-Cx}$ fitted to the mean values of FEV_1 when ipratropium bromide was administered from a metered-dose inhaler (●) and a Wright nebuliser (▲) to a cumulative dose of 72 μg. – – – – indicates estimated dose of ipratropium needed to achieve 99% of the bronchodilator effect.*

chodilatation and dose-response curves with the two modes of administration of ipratropium bromide suggest that equivalent amounts of the drug reached the site of action in the airways on these two occasions. A cumulated dose of 72 μg of ipratropium bromide was estimated from the dose-response curve for FEV_1 (fig 4) to produce about 95% of the maximum bronchodilator response and the principal advantage of a higher dose would be a longer duration of action.[6]

In conclusion, it appears that for patients with a moderate degree of airflow obstruction (mean baseline FEV_1 <45% of predicted) who are experienced users of metered-dose inhalers there is no therapeutic advantage in the use of ipratropium bromide by jet nebulisation. Nevertheless, the administration of the drug by this technique may be of advantage during a severe exacerbation of airflow obstruction, when a patient may be unable to use a metered-dose inhaler efficiently.

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depolarising muscle relaxants were avoided and paralysis was induced with pancuronium. There were no difficulties with ventilation in this period and, although moderate hypothermia is known to potentiate all types of neuromuscular blockade,[3] the patient showed no abnormal requirements or sensitivity to the dose administered and was responding to commands at the end of the procedure. To avoid inducing myotonia we did not use halothane, which commonly produces postoperative shivering.

Another potential difficulty in paramyotonia congenita relates to the electrolyte shifts which may occur with haemodilution and cardiopulmonary bypass. In particular, hyperkalaemia may precipitate myotonia.[1] The primary muscle defect is thought to be related to increased sodium conductance in affected muscles. An infusion of 80 mmol (mEq) of potassium chloride in 500 ml 5% dextrose infused at 80 ml/h was able to prevent gross fluctuations in serum potassium concentrations in this patient.

Only minimal postoperative respiratory depression was seen, with a transient rise in arterial P_{CO_2}. The major postoperative difficulty encountered was the occurrence of brief episodes of hypotension and falling central venous pressures, which were not significantly affected by volume loading or by dopamine infusion. Although the aetiology of these haemodynamic changes is not definitely known, they were possibly related to sudden changes in peripheral resistance or venous capacitance or both. The attacks proved benign, though they did increase the duration of the patient's stay in the intensive care unit.

In summary, cardiopulmonary bypass using moderate hypothermia has been undertaken safely in a patient with paramyotonia congenita. Depolarising muscle relaxants and halothane were avoided, and complete rewarming on bypass was carefully carried out. The anticipated respiratory difficulties did not occur and postoperative recovery was complete.

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Correction

Dose-response comparison of ipratropium bromide from a metered-dose inhaler and by jet nebulisation

In the paper by SA Gomm and others (April, pp 297–301) we regret an error in line 3 of the last paragraph, where "< 45%" should be "> 45%."