Effect of an extension tube on the bronchodilator efficacy of terbutaline delivered from a metered dose inhaler

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ABSTRACT A double-blind within-patient investigation was performed to determine whether the interposition of an extension tube (10 cm length $\times$ 3.2 cm diameter) between a metered dose inhaler and the mouth alters the bronchodilator efficacy of terbutaline sulphate. On two consecutive study days 14 adult patients with stable reversible airways obstruction inhaled a cumulative dose of 500 μ g of terbutaline which was delivered from a metered dose inhaler with or without the extension tube attached and received placebo in a similar manner. The drug was inhaled in doses of 125, 125, and 250 μ g at 20 minutes intervals. The following measurements were made: forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), peak expiratory flow rate (PEFR), thoracic gas volume (TGV), and specific airways conductance (sGaw). These were done immediately before and at five and 15 minute intervals after each dose, and were repeated 90, 120, 180, 240, and 300 minutes after the first inhalation of terbutaline. Administration of terbutaline with and without an extension tube achieved significant bronchodilation at all dose levels in all respiratory variables ($p < 0.001$). There was no statistically significant difference in FEV₁, FVC, PEFR, and sGaw values at any time or dose level with either method of administration. The use of the extension tube did not impair the efficacy or duration of action of inhaled terbutaline.

Pressurised aerosols provide a convenient and rapid method of delivery of drugs into the airways. One of the practical disadvantages associated with the use of freon propelled inhalers is that 70-90% of the dose impacts on the oropharynx, and is subsequently swallowed.^{1,2} Even if the technique of administration is optimum, only 10% of the drug enters the airways. A method recommended to overcome aerosol deposition in the mouth has been to hold the canister a short distance from the widely open mouth.³ Studies by Morén⁴ have shown that the interposition of an extension tube (10 cm length $\times$ 3.2 cm diameter) between the mouth and a metered dose inhaler reduces significantly the total "loss" of drug in the mouth and tube—that is, from 53.9% to 39.6%—thus indicating the possibility of increasing the availability of the drug within the lungs and hence improving its therapeutic effect. It is quantitatively difficult to assess the amount of

aerosol which enters the lungs but a dose-related bronchodilator effect can be assessed by the degree of relief of airways obstruction. The present study was designed to assess the therapeutic benefits that may be derived from the addition of an extension tube (spacer) to a metered dose inhaler in the administration of terbutaline sulphate.

Methods

The study was performed on 14 adult patients (nine male and five female) whose clinical details are summarised in table 1. Their ages ranged from 19 to 66 years. Nine of the subjects had asthma, three had chronic bronchitis, and two showed features of chronic bronchitis and late-onset asthma. Nine patients were non-smokers and five were either current smokers or had only discontinued the habit in the last 12 months. All the patients gave informed consent. Subjects were excluded if they had significant bronchopulmonary disease other than asthma or chronic bronchitis, or had evident disease in any other

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Table 1 Sex, age, duration of respiratory illness, diagnosis, baseline and % predicted FEV₁ of the patients entered into the study⁵

Patient	Sex	Age (yr)	Duration of illness (yr)	Diagnosis	Baseline FEV ₁ (l)	% Predicted FEV ₁
1	M	63	45	A + CB	1.46	44
2	F	51	25	A	1.57	69
3	M	24	6	A	1.32	29
4	M	33	5	A	1.26	34
5	M	41	7	A	1.30	39
6	M	19	18	A	0.98	28
7	M	62	5	CB	1.23	43
8	M	66	5	CB	0.82	30
9	F	52	23	A + CB	1.44	62
10	F	59	12	A	0.94	43
11	M	52	30	CB	0.96	29
12	M	42	2.5	A	1.65	44
13	F	60	10	A	1.27	65
14	M	52	3	A	1.80	64

A = asthma⁶CB = chronic bronchitis⁷

system. All had a baseline FEV₁ which was less than 70% of their predicted normal value⁵ and an improvement in FEV₁ of greater than 20% after inhaling 200 µg salbutamol. In addition, the subjects' FEV₁ did not vary by more than 12.5% between study days. Bronchodilator drugs were discontinued for the 12 hours before each experiment. Patients receiving corticosteroids or disodium cromoglycate continued this treatment during the study.

Terbutaline sulphate was supplied as a conventional pressurised multidose inhaler delivering 125 micrograms per actuation. A cylindrical plastic extension tube referred to as the spacer was attached to the mouthpiece of the inhaler. The spacer was 10 cm long and had a diameter of 3.2 cm throughout its length except at the end where it fitted the inhaler; at this end, radially disposed openings in the spacer allowed the subject to inspire freely while actuation of the inhaler delivered the drug into this airstream.

Each patient visited the respiratory laboratory at the same time on two consecutive days between 0900 and 1500 so that each patient was affected similarly by any diurnal variation in respiratory function. They rested for 30 minutes and control values PEFR, FEV₁, FVC, TGV, airways resistance (Raw), and pulse rate were recorded. Then they received inhalations from two externally identical metered dose inhalers, one of which delivered 125 µg terbutaline per puff and the other propellant only, as placebo. Each inhaler was attached either to a standard mouthpiece or a mouthpiece with the added extension tube. Thus, each subject administered two consecutive inhalations so that only one dose of terbutaline was received, and neither the subject nor the observer knew whether this or

placebo was dispensed via the standard mouthpiece or the spacer.

At 20-minute intervals on each treatment day the patients were given terbutaline in doses of 125 µg, 125 µg, and 250 µg, and at the same time intervals one puff, one puff, and two puffs of placebo. On one day the 500 µg cumulated dose of terbutaline was administered with a conventional adaptor and the placebo via the spacer; on the other study day the spacer was attached to the terbutaline aerosol. The treatment order was randomly allocated and the design of the experiment rendered this double-blind. Measurements of FEV₁, PEFR, and FVC were made on an Ohio 842 spirometer. A pressure-corrected flow plethysmograph (Fenyves and Gut) was used to measure thoracic gas volume and airways resistance,⁸ and the results expressed as the reciprocal of airways resistance per litre of thoracic gas volume, specific airways conductance (sGaw). These recordings were made at five and 15 minute intervals after each dose of terbutaline and then 90, 120, 180, 240, and 300 minutes after the first inhalation. The means of three and five measurements for spirometry and plethysmography respectively were taken as the final results used in our analysis of each index of lung function. Statistical analysis was carried out using a *t* test for paired comparisons.

Results

The administration of terbutaline with or without the extension tube produced significant bronchodilation (*p* < 0.001) at each dose level by all criteria (increase in FEV₁, PEFR, FVC, sGaw, and decrease in TGV). The graded im-

Table 2 Mean increase in FEV_1 (l), $PEFR$ (l/min), and FVC (l) ($\pm$ SD) for 14 patients after inhaling terbutaline

Time (min) Dose of terbutaline	0 —	20 125 μ g	40 125 μ g	60 250 μ g	90 —	120 —	180 —	240 —	300 —
FEV_1 (l)									
A	1.17 (0.34)	1.47 (0.45)	1.57 (0.44)	1.64 (0.64)	1.68 (0.46)	1.68 (0.45)	1.56 (0.40)	1.52 (0.41)	1.50 (0.44)
B	1.17 (0.36)	1.45 (0.40)	1.56 (0.42)	1.66 (0.46)	1.68 (0.46)	1.67 (0.45)	1.60 (0.44)	1.47 (0.37)	1.46 (0.34)
$PEFR$ (l/min)									
A	179 (58)	219 (64)	239 (69)	251 (78)	254 (80)	258 (77)	236 (70)	235 (69)	228 (80)
B	178 (62)	217 (68)	231 (72)	255 (80)	260 (81)	251 (74)	252 (79)	223 (69)	219 (65)
FVC (l)									
A	2.67 (0.72)	3.11 (0.83)	3.22 (0.85)	3.42 (0.85)	3.37 (0.76)	3.38 (0.82)	3.20 (0.74)	3.15 (0.75)	3.13 (0.77)
B	2.58 (0.80)	3.00 (0.67)	3.24 (0.78)	3.13 (0.81)	3.33 (0.77)	3.33 (0.83)	3.23 (0.70)	2.99 (0.59)	3.15 (0.75)

A = normal adaptor, B = extension tube.

Bronchodilatation at each dose level at 20, 40, and 60 min was significant for A and B $p < 0.001$.

provement can be seen in tables 2 and 3 and figs 1 and 2. Comparison of the responses obtained with and without the use of the extension tube, showed that there was no significant difference in the respiratory variables recorded at any dose or time. There was no significant increase in pulse rate and no side effects were noted during the administration of terbutaline. Twelve patients subjectively preferred the use of the tube spacer because of lack of impaction of the aerosol on the tongue; one stated that there was no difference between the two methods, and one preferred the conventional actuator of a metered dose inhaler.

Discussion

The therapeutic efficacy of an inhaled bronchodilator depends, among other things, on the proportion of the inhaled drug which is deposited in the lung and its distribution within the airways. Important factors in aerosol penetration include the technique of inhalation,^{9,10} the size of the particles inhaled,¹¹ and abnormalities in airways structure.^{12,13}

The aim of the present study was to alter the mode of inhalation by the use of an extension tube, thus decreasing the deposition of the drug within the oral cavity and perhaps allowing more

Table 3 Mean decrease in TGV (l) ($\pm$ SD) and mean increase in $sGaw$ ($kPa^{-1}s^{-1}$) for 14 patients after inhaling terbutaline

Time (min) Dose of terbutaline	0 —	20 125 μ g	40 125 μ g	60 250 μ g	90 —	120 —	180 —	240 —	300 —
TGV (l)									
A	4.593 (1.098)	4.375 (1.090)	4.210 (1.123)	4.010 (1.032)	3.980 (1.021)	3.876 (1.107)	4.034 (1.041)	4.080 (1.029)	4.230 (0.922)
B	4.658 (0.861)	4.224 (0.881)	4.155 (0.825)	3.897 (0.914)	3.981 (0.867)	3.943 (0.863)	4.031 (0.938)	4.091 (0.928)	4.202 (0.771)
$sGaw$ ($kPa^{-1}s^{-1}$)									
A	0.347 (0.09)	0.524 (0.20)	0.616 (0.22)	0.727 (0.32)	0.765 (0.36)	0.765 (0.36)	0.657 (0.28)	0.627 (0.23)	0.605 (0.28)
B	0.332 (0.08)	0.515 (0.17)	0.857 (0.26)	0.709 (0.28)	0.765 (0.35)	0.813 (0.40)	0.695 (0.31)	0.603 (0.23)	0.541 (0.28)

A = normal adaptor, B = extension tube.

Improvement in TGV and $sGaw$ at each dose level was significant at 20, 40, and 60 min for A and B $p < 0.001$.

Fig 1 Mean increase in FEV₁ (l) after inhaling 500 µg cumulated dose of terbutaline.

Fig 2 Mean increase in sGaw (kPa⁻¹s⁻¹) after inhaling 500 µg cumulated dose of terbutaline.

drug to enter the airways. The current method of using metered dose inhalers is for each puff to be deeply inhaled and the breath to be held afterwards. The following factors during inhalation influence the effect of the drug within the lung: firstly, a high flow rate during inspiration reduces penetrance because of impaction of particles within the mouth and large airways^{14 15}; secondly, with increasing inspired volume drug penetrance is increased at a constant flow rate¹³ and breath-holding after inspiration allows the particles within the airways to settle by gravity.¹⁶

Moren⁴ concluded that an extension tube attached to an inhaler decreased deposition of aerosol droplets within the mouth by reducing the velocity of particles emitted from the tube, increasing the time for evaporation, and thereby reducing droplet size and allowing better distribution of particles within the airways.

The bronchodilator efficacy of terbutaline in our study was neither impaired nor increased by the use of the tube spacer. A possible reason for the lack of improvement is that 10 of the 14

patients had a baseline FEV₁ less than 45% of their predicted values. This degree of airflow obstruction is associated with premature impaction of aerosol particles caused by disturbed flow.^{12 14 17} Thus, even if there is increased delivery of drug into the trachea, the distribution of the drug to its site of action may be impaired.

However, there may be circumstances where the use of an extension tube in association with metered dose inhalers has advantages. For instance, it is recognised that a proportion of patients use these devices inefficiently,¹⁸ thereby contributing to treatment failure, and Bloomfield *et al*¹⁹ have shown that the use of a tube spacer may compensate partially for an uncoordinated technique of administration. This could be of particular benefit in treating young children who have difficulty operating these inhalers. Also, in the present study 12 out of the 14 patients stated a preference for the addition of the spacer because they experienced less sensation of oral impaction of the aerosol. If their observations are valid, it will be interesting

to see whether the introduction of an extension tube is beneficial for asthmatic patients who have troublesome pharyngeal moniliasis when receiving maintenance corticosteroid aerosol therapy.

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