

Bronchodilator reversibility to low and high doses of terbutaline and ipratropium bromide in patients with chronic obstructive pulmonary disease

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Abstract

Background—There is uncertainty regarding the use of monotherapy or combination therapy with β_2 agonists and anticholinergic drugs in patients with chronic obstructive pulmonary disease (COPD). The measurement of forced expiratory volume in one second (FEV₁) or relaxed vital capacity (RVC) in the assessment of reversibility in these patients has also caused considerable debate.

Methods—Twenty seven patients with COPD were evaluated on two occasions. Patients received the following treatments in sequence: (sequence 1) low dose terbutaline 500 μ g, high dose terbutaline 5000 μ g, low dose ipratropium 40 μ g, high dose ipratropium 200 μ g; (sequence 2) low dose ipratropium 40 μ g, high dose ipratropium 200 μ g, low dose terbutaline 500 μ g, high dose terbutaline 5000 μ g. RVC, FEV₁ and FVC were measured at baseline and 30 minutes after successive treatments.

Results—Values for FEV₁ at baseline on the first and second study days were not significantly different: 0.90 (0.87–0.93) l v 0.90 (0.87–0.93) l. Likewise, baseline values for RVC and FVC were not different. The number of patients showing a greater than 330 ml overall improvement in RVC was 20 of 27 for sequence 1 and 22 of 27 for sequence 2; similar trends were observed for FEV₁ and FVC. For all three parameters there was a significant difference between mean responses to low and high doses of terbutaline when the latter was given as the first drug in sequence 1. When ipratropium was given first in sequence 2 there was, however, no significant improvement with high dose terbutaline over and above the response to low dose terbutaline. The latter effect was more noticeable with RVC than with either FEV₁ or FVC. The total bronchodilator response at the end of each sequence was similar whether ipratropium was given first or second.

Conclusions—The measurement of RVC, FEV₁, and FVC were equally effective at picking up those patients who had a significant overall bronchodilator response to combined therapy with inhaled β_2 agonist and anticholinergic medication. There was no significant benefit of adding a higher dose of terbutaline when ipratropium bromide had been given

previously, particularly when using RVC as the parameter of response.

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Chronic obstructive pulmonary disease (COPD) has a considerable bearing on exercise tolerance and quality of life in those who suffer from it. Optimising the bronchodilator response therefore assumes considerable importance in these patients.

There has been considerable controversy concerning the benefit, or otherwise, of single or combined treatment with inhaled β_2 agonists and anticholinergic drugs in patients with COPD. Several studies have been performed with varying results. However, the majority have only compared either low or high doses of combined treatment without assessing sequential effects of low and high doses of both drugs. There has also been some debate regarding the use of forced expiratory (FEV₁ and FVC) or relaxed (RVC) lung volumes in assessing bronchodilator response in patients with COPD.

Our study had two specific aims. Firstly, to investigate the bronchodilator response to low and high doses of ipratropium and terbutaline given either alone or in combination. Secondly, to assess whether there were any differences between RVC, FEV₁, or FVC in detecting bronchodilator responsiveness.

Methods

PATIENTS

Twenty nine inpatients with COPD were initially recruited into the study. One patient withdrew because of severe tremor following high dose terbutaline and one patient was withdrawn as she was unable to perform pulmonary function tests due to coughing. Twenty seven patients of mean (SE) age 69 (2) years completed the study and were included in the analysis. All patients had recovered following an admission for an acute infective exacerbation of COPD with a mean hospital stay of eight days. All had stable peak flow recordings which had reached a plateau level for at least three days before entry into the study. All patients were studied within 24 hours of discharge from hospital when bronchodilator reversibility testing would normally have been performed. All patients were receiving nebulised salbutamol and oral corticosteroid treatment, with doses remaining unchanged for at least five days before the

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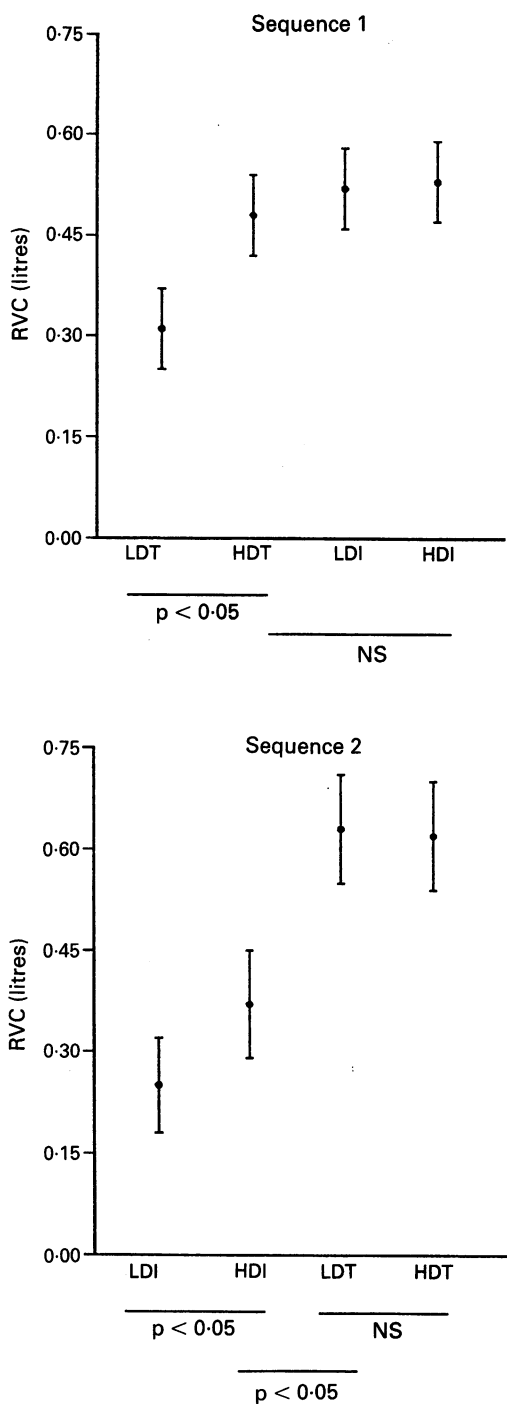
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Figure 1 Effects of sequential inhalation with low dose terbutaline 500 μg (LDT), high dose terbutaline 5000 μg (HDT), low dose ipratropium 40 μg (LDI), and high dose ipratropium 200 μg (HDI) as sequence 1 and the reverse order (LDI, HDI, LDT, HDT) as sequence 2 for RVC. Responses are shown as means and 95% confidence intervals of change from baseline for all 27 patients.



study. Six patients were taking oral theophyllines and three were receiving oral β_2 agonists. All patients were either smokers or ex-smokers and had chronic bronchitis as defined by the Medical Research Council criteria.¹ All patients were required to have an FEV₁ at entry of less than 60% of predicted normal. Care was taken to exclude any patients with a known past history of asthma.² Respiratory function data prior to inclusion in the study are shown in table 1. Measurements of static lung volumes and gas transfer shown in this table were made by helium dilution and single breath carbon monoxide techniques, respectively, using a Morgan transfer test machine (PK Morgan Ltd, Rainham, UK). Approval was given by Tayside ethics committee and informed consent was obtained.

Table 1 Respiratory function parameters in 27 patients with COPD

	Mean (SE)	Range
FEV ₁ (l)	1.02(0.13)	0.7-1.74
FEV ₁ (% predicted)	44(5)	33-51
FVC(l)	1.82(0.22)	1.22-2.54
FVC(% predicted)	64(5)	37-83
FEV ₁ /FVC(%)	55(5)	41-76
RV(% predicted)	121(17.0)	79-139
RV/TLC(%)	55(3)	39-66
TLCO (% predicted)	56(3.1)	39-82

FEV₁—forced expiratory volume in one second; FVC—forced vital capacity; RV—residual volume; TLC—total lung capacity; TLCO—carbon monoxide transfer factor.

All inhaled bronchodilator therapy was withheld for at least 12 hours before each study day and oral β_2 agonists and theophyllines were withheld for 24 hours. Patients were assessed on consecutive days and treatments were given so that the patients but not the investigators were blind to the drugs administered. Patients only proceeded with the second day if baseline FEV₁, FVC, and RVC measurements were within 15% of levels measured on the first day, and all patients recruited were able to be studied on consecutive days.

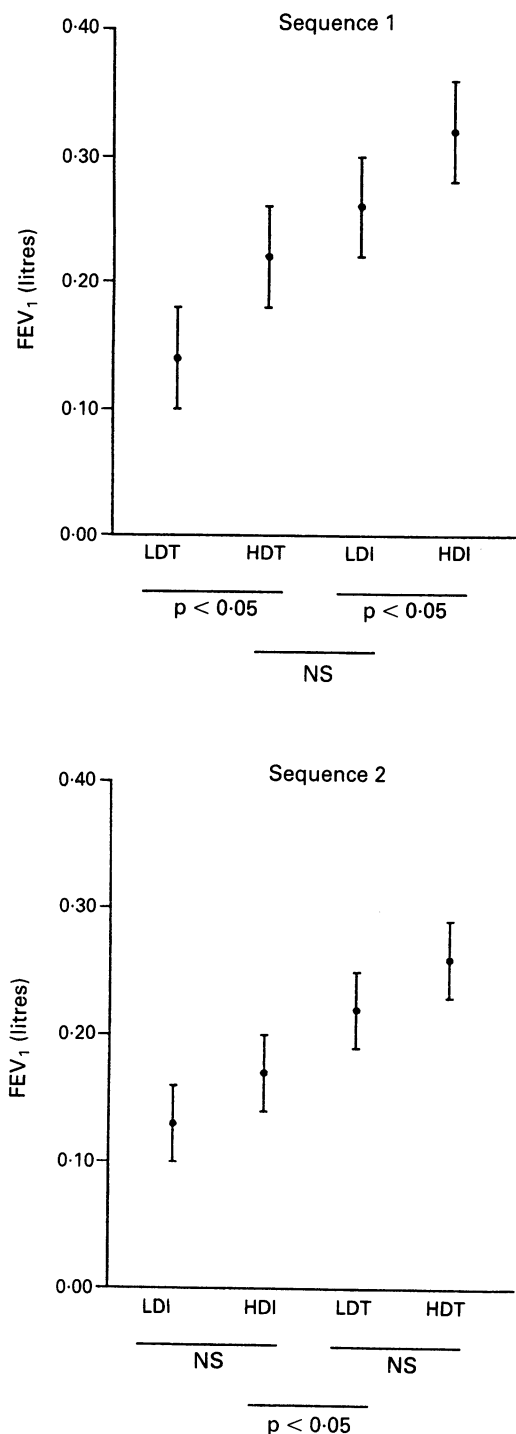
On one occasion all patients received the following order (sequence 1): (i) low dose terbutaline 500 μg given as two puffs of 250 μg per actuation (Bricanyl, Astra Pharmaceuticals), (ii) high dose terbutaline 5000 μg given as five puffs of 1000 μg per actuation (prepared by Astra Pharmaceuticals), (iii) low dose ipratropium bromide 40 μg given as two puffs of Atrovent 20 μg per actuation (Boehringer Ingelheim), (iv) high dose ipratropium bromide 200 μg given as five puffs of Atrovent Forte 40 μg per actuation. On a second occasion the order was reversed with ipratropium being delivered first—that is, low dose ipratropium, high dose ipratropium, low dose terbutaline, high dose terbutaline (sequence 2). All drugs were delivered by metered dose inhaler via a 750 ml pear shaped spacer device (Nebuhaler, Astra Pharmaceuticals) to eliminate individual differences in inhaler technique, using a modification of the method described by Gleeson and Price³ with five deep breaths taken for each actuation of the inhaler.

At baseline and 30 minutes after each successive dose, measurements of forced expiratory lung volumes (FEV₁, FVC) and relaxed vital capacity (RVC) were performed according to American Thoracic Society criteria⁴ using a Vitalograph compact spirometer (Vitalograph Ltd, Buckingham, UK). RVC was performed as a slow forced manoeuvre from total lung capacity.⁵ A coefficient of variation of less than 3% for three reproducible measurements of FEV₁, FVC, or RVC was considered as being acceptable.⁴

STATISTICAL ANALYSIS

Data (as a change from baseline) were

Figure 2 Effects of sequential inhalation of low and high doses of terbutaline and ipratropium on FEV₁ responses as in fig 1.



analysed using a Statgraphics software package (STSC Software Publishing Group, Maryland, USA). RVC was chosen as the primary end point before the study as a basis for calculating sample size. A change in RVC of 330 ml was used as the value required to exclude short term biological variability with 95% confidence.⁶ The use of 27 subjects was sufficient to detect a mean difference of 330 ml between treatments with greater than 80% power ($\beta = 0.20$), α being set at 0.05. Furthermore, the power of the study was at least 80% for detecting a difference in FEV₁ of 160 ml and FVC of 330 ml using 27 subjects. Mean responses were compared by multifactorial analysis of variance (ANOVA) to establish any significant overall effect between all four treatments on each day. In the presence of a significant overall ANOVA, Duncan's multiple range testing with 95% confidence limits was used to identify where differences were significant.⁷ A probability level of $p < 0.05$ was considered as being of significance for all tests.

Results

Mean responses for RVC, FEV₁, and FVC in all 27 patients are shown in figs 1, 2, and 3 respectively, and in table 2. All data are given as changes from baseline shown as means and 95% confidence intervals.

Values for FEV₁ at baseline were not significantly different on the first and second study days: 0.90 (0.87-0.93) l v 0.90 (0.87-0.93) l. Likewise values for RVC 2.06 (2.02-2.10) l v 2.08 (2.04-2.12) l, and for FVC 1.71 (1.64-1.78) l v 1.74 (1.67-1.81) l were not different on the two study days.

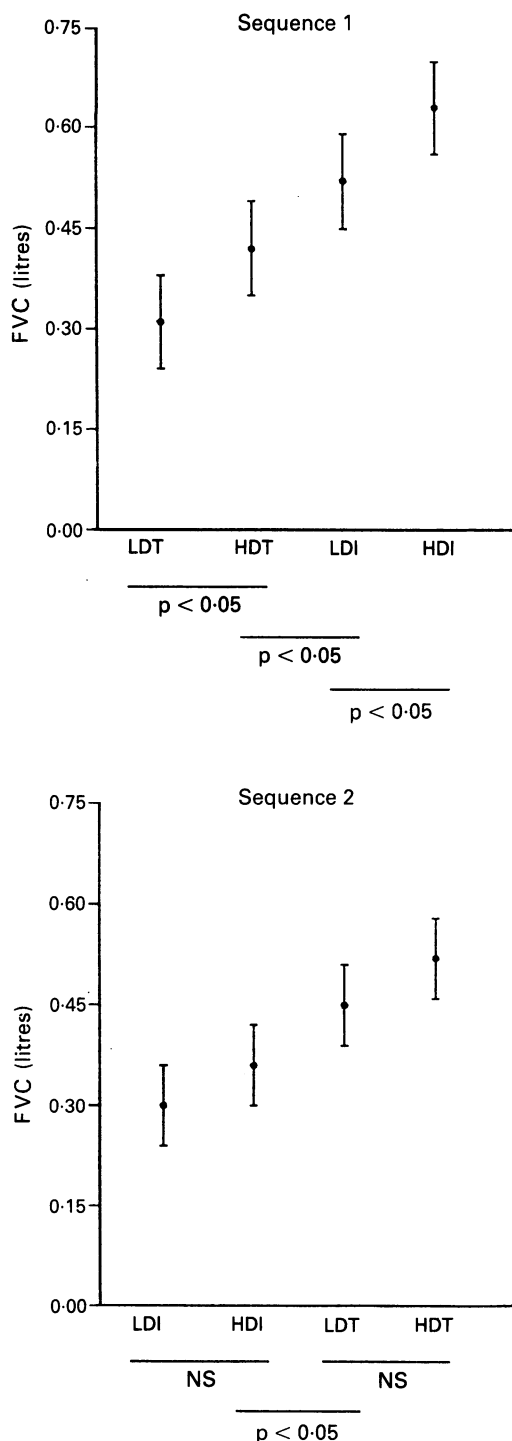
The number of patients who had a greater than 330 ml overall improvement in RVC was 20 of 27 in sequence 1 and 22 of 27 in sequence 2. Similar numbers of responders were observed for FEV₁ (> 160 ml change): 21 of 27 in sequence 1 and 22 of 27 in sequence 2. The figures for FVC were identical to those of RVC. Of those who failed to respond on either day, all were current smokers with an FEV₁ < 40% predicted normal, all had a TLCO < 50% predicted normal, and all had an increased RV and RV/TLC with a

Table 2 Mean (95% CI) values in all 27 patients as change from baseline for RVC, FEV₁ and FVC after sequential treatments with low and high doses of terbutaline and ipratropium bromide shown as sequence 1 and sequence 2

Sequence 1				
	Low dose terbutaline (500 µg)	High dose terbutaline (5000 µg)	Low dose ipratropium (40 µg)	High dose ipratropium (200 µg)
RVC (l)	0.31 (0.25-0.37)	0.48 (0.42-0.54)	0.52 (0.46-0.58)	0.53 (0.47-0.58)
FEV ₁ (l)	0.14 (0.10-0.18)	0.22 (0.18-0.26)	0.26 (0.22-0.30)	0.32 (0.28-0.36)
FVC (l)	0.31 (0.24-0.38)	0.42 (0.35-0.49)	0.52 (0.45-0.59)	0.63 (0.56-0.70)
Sequence 2				
	Low dose ipratropium (40 µg)	High dose ipratropium (200 µg)	Low dose terbutaline (500 µg)	High dose terbutaline (5000 µg)
RVC (l)	0.25 (0.18-0.32)	0.37 (0.29-0.45)	0.63 (0.55-0.71)	0.62 (0.54-0.70)
FEV ₁ (l)	0.13 (0.10-0.16)	0.17 (0.14-0.20)	0.22 (0.19-0.25)	0.26 (0.22-0.30)
FVC (l)	0.30 (0.24-0.36)	0.36 (0.30-0.42)	0.45 (0.39-0.51)	0.52 (0.46-0.58)

RVC—relaxed vital capacity; FEV₁—forced expiratory volume in one second; FVC—forced vital capacity.

Figure 3 Effects of sequential inhalation of low and high doses of terbutaline and ipratropium on FVC responses as in fig 1.



pressure dependent pattern on flow-volume loop—that is, features which are consistent with a large component of emphysema.

During sequence 1 low dose terbutaline produced a significant ($p < 0.001$) increase in RVC, with further significant ($p < 0.05$) improvement occurring after high dose terbutaline. However, the addition of ipratropium bromide produced no further significant change irrespective of dose. For sequence 2 the RVC response to low dose ipratropium was significant ($p < 0.001$), with high dose ipratropium conferring a small further benefit ($p < 0.05$). The addition of low dose terbutaline also gave rise to a significant ($p < 0.05$) improvement, whereas high dose terbutaline produced no further increase.

Mean responses to FEV₁ showed similar overall trends to RVC. In sequence 1 low dose terbutaline produced a significant ($p < 0.001$) increase in FEV₁, with further improvement ($p < 0.05$) occurring with high dose terbutaline. The addition of high dose but not low dose ipratropium produced a significant ($p < 0.05$) increase above the response to high dose terbutaline. For sequence 2 the response to low dose ipratropium was significant ($p < 0.001$), with no further change after high dose ipratropium. The addition of low dose but not high dose terbutaline produced a further significant ($p < 0.05$) increase.

For FVC, in sequence 1 low dose terbutaline produced a significant ($p < 0.001$) increase, with a further significant ($p < 0.05$) improvement on adding high dose terbutaline. The subsequent addition of low dose and high dose ipratropium both produced further significant increases ($p < 0.05$ and $p < 0.05$, respectively). For sequence 2 the response to low dose ipratropium was significant ($p < 0.05$) with no additional benefit conferred by high dose ipratropium. A significant ($p < 0.05$) additional improvement occurred, however, on adding low dose terbutaline but not high dose terbutaline.

Discussion

The results of this study showed that RVC, FEV₁, and FVC were equally effective at identifying overall responders to combined therapy with β_2 agonist and anticholinergic medication. For all three parameters there was a dose-response effect between low and high doses of terbutaline when given as the first drug. However, when ipratropium bromide was given first, there was no significant improvement with high dose terbutaline over and above the response to the lower dose. This effect was more noticeable with RVC than with either FEV₁ or FVC. It is important to distinguish between studies involving patients with acute or stable airflow obstruction, and the results of the present study should not, therefore, be extrapolated to the setting of acute exacerbations of COPD. Furthermore, the data presented are from a single dosing study and caution is advised in extending the current results to effects of long term treatment.

In patients with stable, moderate to severe COPD, inhaled ipratropium bromide in low doses has been shown to produce a more pronounced bronchodilator response than inhaled β_2 agonist in single dosing or chronic dosing studies.^{8,9} Other similar studies, which have only compared either low or high doses of both agents, have suggested that either combined treatment produces an optimal bronchodilator response,^{10,11} or that monotherapy confers as much benefit as combined therapy.^{12,13} It has been suggested that the ageing process is accompanied by a decline in β_2 receptor function in the airways of patients with COPD.^{14,15} However, there is no evidence to suggest that impaired respon-

siveness of peripheral β_2 receptors occurs in the elderly.¹⁶ Furthermore, there is a steep airways dose-response relationship with inhaled β_2 agonists in elderly patients with COPD.¹⁷

The doses used in the study were chosen specifically to demonstrate responses at a conventional dose and a dose likely to reach the top of the dose-response curve. To increase the likelihood of detecting a significant response in our patients, parameters were measured at a time when a peak bronchodilator response occurred. Previous studies in patients with COPD have shown that the peak bronchodilator response occurs at approximately 30 minutes for both ipratropium and salbutamol.^{18,19} It was also important that patients be studied when their airflow obstruction was stable, and this was shown in two ways. Firstly, mean baseline values for all parameters measured were virtually identical and secondly, all patients studied underwent sequences 1 and 2 on consecutive days as individual baseline values did not vary by more than 15%. Although all patients were taking oral corticosteroids, doses had remained stable for at least five days and, indeed, it has been shown previously that acute dosing with oral corticosteroids does not have a significant effect on bronchodilator responsiveness in patients with COPD.²⁰

It was particularly interesting to find that the mean response to high dose terbutaline appeared to vary depending on whether it was given before or after ipratropium. High dose terbutaline significantly improved mean responses for RVC, FEV₁, and FVC over and above the standard dose of terbutaline in the presence of normal vagal tone during sequence 1, but added little when vagal tone was attenuated by ipratropium as in sequence 2. The explanation for these findings is not entirely clear but cannot simply be explained by airways geometry alone. Giving terbutaline as initial therapy gives rise to a dose-response effect, although the prevailing vagal tone would appear to prevent optimum achievable dilatation being attained, since the subsequent addition of ipratropium still achieves a further small degree of bronchodilatation. However, in most cases prior attenuation of vagal tone by ipratropium permits optimal achievable dilatation to be attained by subsequent inhalation with low dose terbutaline alone. In effect, therefore, a flattening of the dose-response curve to terbutaline may occur when vagal tone is attenuated. It is also worth mentioning that there are prejunctional inhibitory β_2 receptors on cholinergic fibres which might conceivably result in attenuation of resting vagal tone, in addition to direct β_2 mediated smooth muscle relaxation.²¹

In the present study the number of overall responders was equally detected by using FEV₁, FVC, or RVC. However, it was evident that, although there was no significant difference between low and high doses of terbutaline in sequence 2, this effect was most apparent when measuring RVC. This sug-

gests that RVC should be used in conjunction with FEV₁ in assessing the dose required to optimise bronchodilator response. This is in keeping with other studies which have also shown RVC to be a useful parameter in detecting significant bronchodilator reversibility for those patients with COPD who do not show a significant FEV₁ response.^{6,22-25}

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