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Effect of terbutaline on mucociliary clearance in asthmatic and healthy subjects after inhalation from a pressurised inhaler and a dry powder inhaler

Jann Mortensen, Steffen Groth, Peter Lange, Flemming Hermansen

Abstract

Background **β Agonists have been shown to increase mucociliary clearance in some studies but not all. Whether the formulation of β agonists affects mucociliary clearance is not known but may be important as the use of dry powder inhalers increases.**

Methods **The effect of different methods of administration of inhaled terbutaline on mucociliary clearance and forced expiratory volume in one second (FEV_1) was assessed in 10 patients with asthma and 10 healthy subjects. Terbutaline (1 mg) was administered through a metered dose inhaler with a spacer (Nebuhaler) or a dry powder inhaler (Turbuhaler), or both treatments were given, in a four way double blind, double dummy trial. Mucociliary clearance was measured by bronchoscintigraphy.**

Results **Clearance of radioactivity from the lobar bronchi increased in the asthmatic patients by a median of 32% after terbutaline was given by metered dose inhaler and 55% after a combined dose of 2 mg from both inhalers (1 mg from each) compared with placebo but by only 9% after 1 mg of terbutaline was given by a dry powder inhaler. In the healthy subjects mucociliary clearance increased by 51% when terbutaline was given by a dry powder inhaler, by 66% when given by a metered dose inhaler, and by 66% when given by both inhalers combined. The effect of terbutaline on FEV_1 was the same with each of the inhalers.**

Conclusion **Despite similar changes in FEV_1 with the two formulations terbutaline increased mucociliary clearance significantly in asthmatic and healthy subjects when inhaled from a metered dose inhaler whereas when it was inhaled from a dry powder inhaler its effect was significant only in healthy subjects. The reason for the difference in asthmatic subjects is unclear, but may be associated with differences in the deposition of terbutaline.**

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Mucociliary clearance, one of the most important defence mechanisms in the lung, is believed to be of special importance in patients with asthma, in the defence against allergens, infections, and irritants and for clearance of airway secretions.[1] It may, however, be impaired in such patients.[2] Attempts have been made to develop drugs which increase mucociliary clearance. β_2 Adrenergic agonists have a dose dependent effect on the frequency of ciliary beats in vitro.[3–5] Studies of their effect on mucociliary clearance in humans have, however, had conflicting results.[1 2 6–21] The drugs have a beneficial effect on lung function and are widely used to treat patients with asthma. They are often given by pressurised metered dose inhalers, which contain chlorofluorocarbons, although these are likely to be replaced in the future by metered dose inhalers with alternative propellants or with other portable devices for aerosolising drugs, such as dry powder inhalers. The terbutaline dry powder inhaler (Bricanyl Turbuhaler) is one such device.[22]

We compared mucociliary clearance and forced expiratory volume in one second (FEV_1) in healthy subjects and patients with mild to moderate bronchial asthma after inhalation of equal doses of terbutaline from a metered dose inhaler with a spacer (Nebuhaler) and from a dry powder inhaler. Mucociliary clearance was measured by a non-invasive radioaerosol technique—bronchoscintigraphy[6]—which allows visualisation of the rate of disappearance of centrally deposited radioactivity from the large airways.

Methods

SUBJECTS

Ten asthmatic subjects (five men and five women) and 10 healthy subjects (three men and seven women) participated in the study. All gave their fully informed consent and the study was approved by the medical ethics committee of Copenhagen. The median age of the asthmatic subjects was 36·5 years (range 22–69 years) and of the healthy controls 30·5 years (22–63 years). All of the asthmatic subjects had a history of repeated episodes of wheezing and dyspnoea, spontaneous peak flow variations of at least 20%, and an increase of at least 15% in FEV_1 after inhalation of a β_2 agonist. All were currently being treated with an inhaled β_2 agonist or steroid, or both (five with β_2 agonists and steroid, four with β_2 agonists alone, and one with steroids only). All drugs, except inhaled steroids, were withheld for the 12 hours preceding each study day. One asthmatic subject was a current smoker (30 pack years).

Five subjects (four asthmatic and one control) had stopped smoking 10–50 years before the study (1–18 pack years). The other 14 were lifelong non-smokers.

RADIOAEROSOL PROCEDURE

Subjects inhaled an ultrasonically nebulised (by a DeVilbiss 35 B) aerosol of albumin labelled with technetium-99m and isotonic saline[6] according to the following technique. Inhalation, limited to a volume of 750 ml, started at residual volume. The radioaerosol was given as a bolus in the last 250 ml. The mass median aerodynamic particle diameter of the droplets from the nebuliser was 3·4 μm (standard deviation 1·9 μm). The inhaled flow rate was monitored by a pneumotachograph and displayed on line on a computer screen. Subjects were instructed to keep the inhaled flow rate between 200 and 300 ml/second. After the 750 ml was inhaled they immediately exhaled forcefully without any holding of breath. They made 30 to 45 inhalations until about 700 counts/second was obtained from a large field of view gammacamera.[6] Immediately after the radioaerosol inhalation the initial distribution of deposited particles in the lungs was visualised by a posteriorly positioned camera. Subjects were seated against the camera in a chair that was specially designed to limit movement during the five minute counting periods. For the next two hours 10 gammacamera readings were obtained at regular intervals (for each 10–15 minutes). Each bronchoscintigram was made of comparable intensity by adjusting the acquisition time to compensate for the physical decay of ^{99m}Tc.[6] Mucociliary clearance was assessed by independent inspection of the bronchoscintigrams by two authors (JM and SG), who were unaware of which medication had been given. The assessment included counting the number of bronchi that could be identified and noting the time after inhalation when they could no longer be seen. In addition, a semiquantitative estimation of relative mucociliary clearance rates on each of the four study days was made for each subject and ranked as the slowest transport (4), second slowest (3), second fastest (2), and fastest (1).

In addition, mucociliary clearance was assessed by a conventional method. All images were recorded in 64 × 64 pixels and stored in the computer (General Electric Star). After correction for background and physical decay, clearance was derived from the radioaerosol retention at 120 minutes after the start in the whole lung and in the peripheral zone (fig 1) as a percentage of the initial reading.

Krypton-81m ventilation scintigraphy was used to define the lung outline and lung zones (fig 1) and to calculate a penetration ratio (the ratio of peripheral to central zone radioactivity due to ^{99m}Tc[23]). The zones were created after visual inspection of the central airways in bronchoscintigrams so that the central zone (17% of the total pixels) covered mainly the trachea and main bronchi; the intermediate zones (24% of the pixels) mainly lobar, segmental, and subsegmental bronchi; and the peripheral zones (59% of the pixels) the more peripheral bronchial generations. Each zone contained alveoli. As indicated by ^{81m}Kr ventilation scintigraphy the proportions of alveolar volume in the central, intermediate, and peripheral zones were about 15%, 33%, and 51% respectively.

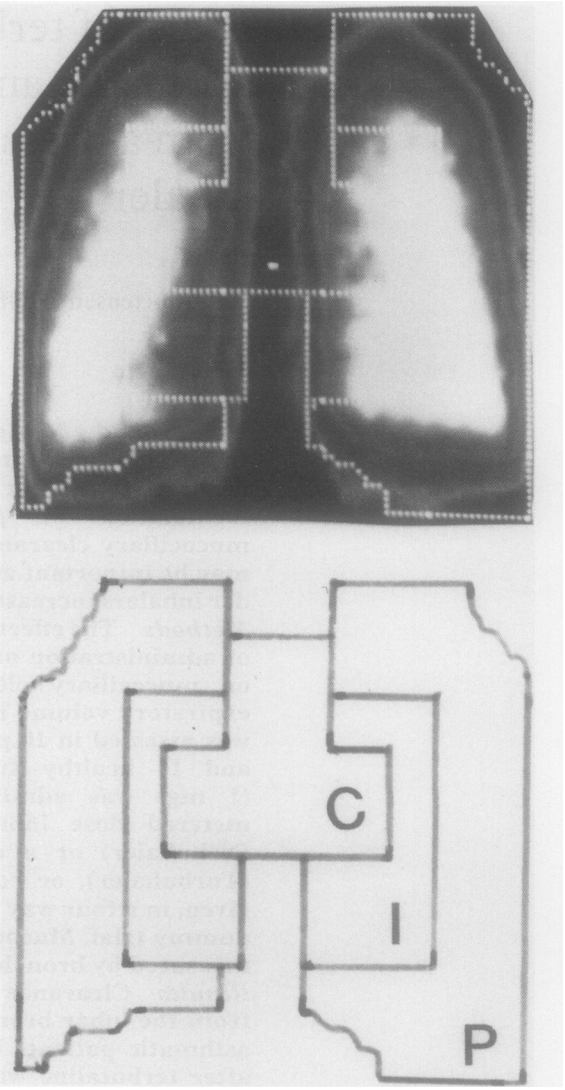

Figure 1 Central (C), right and left intermediate (I), and right and left peripheral (P) lung zones defined by ^{81m}Kr ventilation scintigraphy.

PROTOCOL

The effect of terbutaline sulphate on mucociliary clearance was studied by using a randomised, four part, double blind, double dummy protocol. The drug doses delivered on the four days by the metered dose inhaler and the dry powder inhaler were: placebo through both inhalers; 1 mg of terbutaline through the metered dose inhaler and placebo through the dry powder inhaler; placebo through the metered dose inhaler and 1 mg of terbutaline through the dry powder inhaler; and 1 mg of terbutaline through both inhalers. The placebo metered dose inhaler canister contained the usual lubricants and chlorofluorocarbons, whereas the placebo dry powder inhaler contained nothing. In this way the amounts of propellant and lubricant inhaled were constant on the four days. The drug or placebo was inhaled immediately after the deposition of the

^{99m}Tc albumin had been verified by the first bronchoscintigram. Both were administered as four puffs from the metered dose inhaler (0·25 mg of terbutaline per puff) attached to a pear shaped spacer (Nebuhaler, Astra) and two inhalations from the dry powder inhaler (0·5 mg of terbutaline per inhalation). The patients were instructed to take one deep slow inhalation from the residual volume after two puffs had been released from the metered dose inhaler into the spacer and to hold their breath for 10 seconds before exhalation. This was repeated one minute later. Inhalation from the dry powder inhaler was then performed as a forced deep inhalation from residual volume followed by holding of breath before exhalation. One minute later the inhalation was repeated.

LUNG FUNCTION

All recordings were made on a pneumotachograph (Jaeger Transfer Screen). On each study day flow volume curves were obtained before the bronchoscintigraphic investigation to ensure that the FEV_1 varied by less than 15% between days. After each bronchoscintigraphic investigation—that is, 120 minutes after the inhalation of terbutaline or placebo—flow volume measurements were repeated. The highest of three technically satisfactory measurements was used.

STATISTICAL ANALYSIS

Comparison of data among the four study days was performed by Friedman analysis of variance by ranks or by the Page test for trend.[24] Subsequently, matched paired data were analysed by the Wilcoxon rank sum test. Comparisons between the asthmatic subjects and the healthy subjects were made by the Mann-Whitney U test. Spearman's test was used for correlation analysis.

Results

LUNG FUNCTION

Median (range) baseline FEV_1 was 90·5% predicted value (41–124%) in the patients with asthma and 132% (109–145%) in the healthy subjects. There was no significant difference in baseline FEV_1 among the four study days in either group (fig 2). In the asthmatic subjects there was a mean increase in FEV_1 of 0·6 litres (28%) above baseline 120 minutes after inhalation of terbutaline ($p < 0·01$). The increase was similar for terbutaline administered by the metered dose inhaler or the dry powder inhaler, or both. In the healthy subjects the mean increase in FEV_1 after terbutaline was only 0·2 litres (5%).

There was no significant difference among the penetration ratios on the four days in healthy or asthmatic subjects (table 1). None of the subjects had a productive cough during the examination. The median numbers of non-productive coughs per study period in the asthmatic subjects did not differ significantly with the inhaler used: 0·5 with placebo in both inhalers, 0·3 with the drug given by metered dose inhaler, 0·1 with the drug given by dry powder inhaler, and 0·2 with the drug given by both inhalers. Coughing in the healthy subjects was negligible (median 0·1–0·2 coughs per study period).

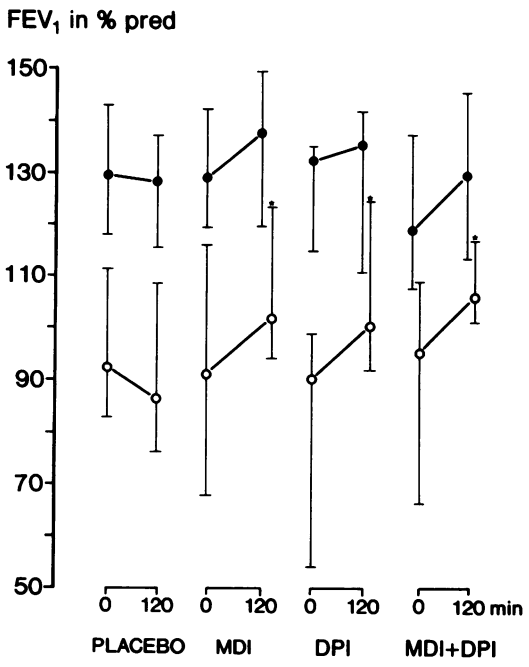

Figure 2 Median FEV_1 % predicted at baseline and 120 minutes after terbutaline or placebo was given on four study days in healthy (closed circles) and asthmatic (open circles) subjects ($p < 0·05$; bars are upper and lower quartiles).*

BRONCHOSCINTIGRAPHY

The trachea, main bronchi, and the five lobar bronchi were visualised in all subjects on each of the four study days. The median number of segmental bronchi visualised was 13 after treatment with placebo, drug given by metered dose inhaler, and drug given by both inhalers and 12 after drug given by dry powder inhaler in the asthmatic subjects, and 11 after treatment with placebo and drug given by metered dose inhaler and 13 after drug given by dry powder inhaler and both inhalers in the healthy subjects. The median difference between the maximum and minimum number of segmental bronchi visualised in the subjects' four bronchoscintigrams was three (range one to six) in the asthmatic subjects and two (zero to 10) in the healthy subjects.

Table 2 shows the individual estimates of mucociliary clearance of the central airways from inspection of the bronchoscintigrams. In the asthmatic subjects mucociliary clearance was similar after terbutaline given by dry powder inhaler and placebo and faster after terbutaline given by metered dose inhaler and by both inhalers. In the healthy subjects mucociliary clearance was fastest after terbutaline given by metered dose inhaler and by both inhalers, slower after terbutaline given by dry powder inhaler and slowest after placebo. The difference in mucociliary clearance between terbutaline given by metered dose inhaler and terbutaline given by both inhalers was not significant in either group.

Table 1 Median (lower and upper quartiles) penetration ratio (peripheral/central zone activity) on four study days

	Placebo	Metered dose inhaler	Dry powder inhaler	Metered dose inhaler plus dry powder inhaler
Asthmatic subjects	0·88 (0·79, 1·02)	0·93 (0·78, 1·02)	0·93 (0·85, 1·00)	0·94 (0·78, 1·01)
Healthy subjects	0·98 (0·90, 1·19)	0·94 (0·83, 1·10)	1·12 (0·96, 1·24)	0·98 (0·89, 1·06)

Table 2 Rank listing of rates of disappearance of radioactivity from segmental, lobar, and main bronchi and trachea from bronchoscintigrams in asthmatic and healthy subjects (fastest clearance ranked 1, slowest ranked 4)

Subject No	Placebo	Metered dose inhaler	Dry powder inhaler	Metered dose inhaler plus dry powder inhaler
		Asthmatic subjects		
1	3·5	2·0	3·5	1·0
2	2·0	1·0	4·0	3·0
3	4·0	2·0	3·0	1·0
4	3·5	3·5	2·0	1·0
5	4·0	3·0	2·0	1·0
6	3·5	1·0	3·5	2·0
7	4·0	1·0	3·0	2·0
8	3·0	1·5	4·0	1·5
9	4·0	1·5	3·0	1·5
10	2·5	2·5	2·5	2·5
Median	3·5	1·8*†	3·0	1·5*‡
		Healthy subjects		
11	4·0	1·5	3·0	1·5
12	4·0	2·0	3·0	1·0
13	4·0	2·0	3·0	1·0
14	4·0	2·5	1·0	2·5
15	4·0	1·0	2·5	2·5
16	4·0	1·0	2·5	2·5
17	4·0	1·5	3·0	1·5
18	4·0	2·0	3·0	1·0
19	4·0	1·5	3·0	1·5
20	3·5	2·0	3·5	1·0
Median	4·0	1·8*†	3·0**	1·5*†

*p < 0·01 compared with placebo.
†p < 0·05 compared with dry powder inhaler, ‡p < 0·01 compared with dry powder inhaler.

Table 3 Last time (minutes) at which the lobar bronchi (mean for five lobar bronchi) were seen in asthmatic and healthy subjects

Subject No	Placebo	Metered dose inhaler	Dry powder inhaler	Metered dose inhaler plus dry powder inhaler
		Asthmatic subjects		
1	77	56	98	25
2	78	51	114	90
3	120	37	84	57
4	111	102	45	48
5	114	81	33	24
6	114	69	120	84
7	120	24	92	30
8	57	46	96	44
9	120	16	24	18
10	108	120	120	120
Median	113	54*	94	46*‡
		Healthy subjects		
11	114	16	24	18
12	105	78	93	42
13	105	37	48	34
14	114	37	28	39
15	120	66	84	93
16	111	51	72	75
17	120	33	57	37
18	111	22	31	16
19	84	28	42	28
20	45	24	54	22
Median	111	35*‡	51*	36*†

*p < 0·01 compared with placebo.
†p < 0·05 compared with dry powder inhaler, ‡p < 0·01 compared with dry powder inhaler.

Table 3 gives the times the lobar bronchi were last seen in the bronchoscintigrams. The times for the asthmatic patients and healthy subjects were similar apart from the longer time for the asthmatic patients after terbutaline given by dry powder inhaler, which approached significance (94 minutes *v* 51 minutes; p = 0·06). The time taken to clear radioactivity from the lobar bronchi in the asthmatic patients was not significantly faster (median 9%) after terbutaline given by the dry powder inhaler than after placebo (median Σ (dry

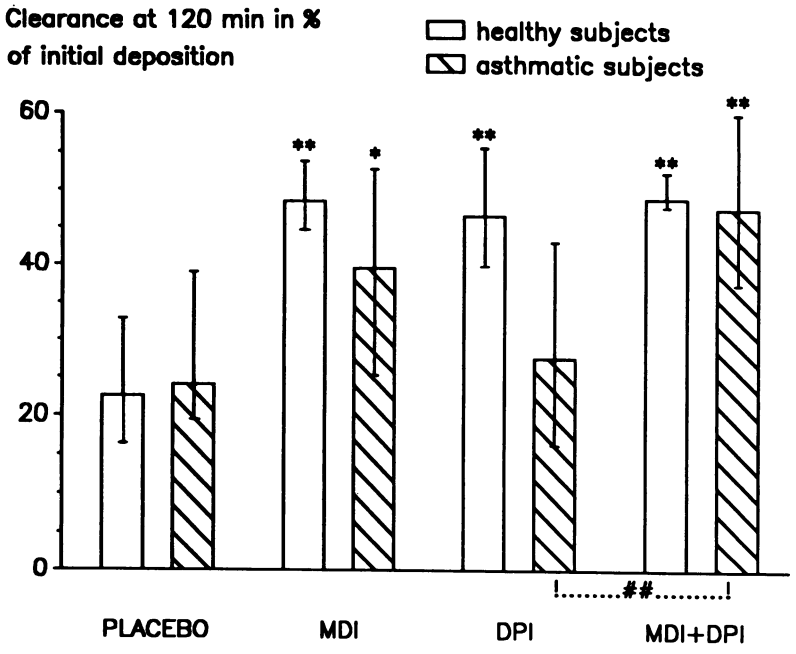

*Figure 3 Percentage of initial deposition cleared at 120 minutes on four study days in healthy and asthmatic subjects (*p<0·05; **p<0·01 compared with placebo; ##p<0·01 between terbutaline treatments; bars are median, upper and lower quartiles).*

powder inhaler −placebo)/placebo × 100%); this was compared with a 32% faster clearance after terbutaline given by the metered dose inhaler ($p < 0·05$) and 55% after terbutaline given by both inhalers ($p < 0·05$). In the healthy subjects the increase in clearance after terbutaline compared with placebo was 51% with the dry powder inhaler ($p < 0·05$), 66% with the metered dose inhaler, and 66% with both inhalers ($p < 0·05$).

LUNG CLEARANCE AT TWO HOURS

When total lung clearance at 120 minutes was compared in the healthy subjects and asthmatic patients (fig 3) the only significant difference was that the value after terbutaline given by dry powder inhaler in the asthmatic subjects was lower than that in healthy subjects ($p < 0·05$).

The median (range) peripheral lung zone clearance at 120 minutes in the asthmatic subjects was 27% with placebo (14–52%), 26% (16–49%) with drug given by dry powder inhaler, 32% (23–43%) with drug given by metered dose inhaler, and 36% (17–50%) with drug given by both inhalers (page test, $p < 0·05$). The corresponding values in the healthy subjects were 18% (12–28%) 32% (25–58%), 34% (24–40%), and 32% (25–48%) ($p < 0·05$ for each drug treatment compared with placebo). Clearance was greater when terbutaline was given by metered dose inhaler than when given by dry powder inhaler in the asthmatic subjects ($p < 0·05$). The asthmatic patients showed a slightly greater peripheral lung zone clearance after placebo than healthy subjects (median 8%; 95% confidence interval 1–18%) and a lower clearance value after terbutaline given by dry powder inhaler (9%; 1–20%).

Neither baseline FEV_1 nor the change in FEV_1 correlated with mucociliary clearance after placebo or with the increase in mucociliary clearance after any of the terbutaline treatments.

Discussion

The results show that the effect of terbutaline on mucociliary clearance in the asthmatic subjects was different when a metered dose inhaler and a dry powder inhaler were used. This was despite similar doses of terbutaline being administered and similar bronchodilatation being seen after terbutaline was given by both inhalers. With the doses given the plateau of the bronchodilator dose-response curve was probably reached, so that a similar degree of bronchodilatation does not necessarily imply that equal doses of terbutaline were deposited in the airways.

How can this lack of mucociliary stimulation from terbutaline given by dry powder inhaler in asthmatic patients be explained? Radioaerosol deposition pattern, numbers of coughs, baseline lung function, and amounts of inhaled aerosolised propellants and lubricants were well matched on the four study days. The fraction of drug deposited in the lung was not measured. Radiolabelled marker techniques have suggested that about 14% of the dose from a dry powder inhaler[25] and 13% of the dose from a metered dose inhaler with a spacing device (Nebuhaler prototype) enter the lungs.[26] The particle size of terbutaline from a metered dose inhaler when leaving the Nebuhaler has not been measured, but is likely to be slightly smaller than the mass median aerodynamic particle diameter of 3·7 μm for the particles leaving the metered dose inhaler because of evaporation of propellants and trapping of the largest particles on the Nebuhaler wall.[27] Terbutaline particles inhaled from a dry powder inhaler are somewhat larger (33–50% of the particles being <5·5 μm and more than 10% being > 10 μm,[25 28] and they may grow hygroscopically after entering the airways.[29 30] In addition, inhalation from the metered dose inhaler with the Nebuhaler was slow compared with that from the dry powder inhaler (60 litres/minute as recommended by the manufacturer). Previous data suggest that the deposition is predominantly central in the lungs of asthmatic patients.[25] These authors studied a similar inhalation procedure (with breath held for 10 seconds) to the one we used (with no holding of breath) and found a deposition of radiolabelled terbutaline with the dry powder inhaler of 39%, 23%, and 37% in central, intermediate, and peripheral zones respectively. The relative areas (pixels) were 13%, 26%, and 61%. These figures suggest a more central distribution than that of ^{99m}Tc albumin in our subjects (25%, 39%, and 36% in the respective zones). It is likely therefore, considering the probable differences in particle size and inhalation rates, that terbutaline when administered by a dry powder inhaler tends to deposit in aggregates in the large airways and oropharynx (72% in the oropharynx[25]) compared with a more diffuse deposition in the airways when the drug is administered by a

metered dose inhaler and spacer (57% in the oropharynx[26]).

If terbutaline given by a dry powder inhaler deposits predominantly in the central airways it would be expected that centrally deposited ^{99m}Tc albumin would clear effectively. However, the peripheral mucociliary clearance was significantly (and whole lung clearance non-significantly) smaller with the dry powder inhaler than with the metered dose inhaler in the asthmatic subjects. This delayed clearance of mucus from the periphery may affect subsequent transport through central airways by failing to supply mucus at the usual rates.[8]

The study of mucociliary clearance was carried out by using a new bronchoscintigraphic method, which allows regional mucociliary clearance to be visualised as the movement of radioactivity in selected central bronchi.[6 7] We also used a conventional computer based measurement of total lung clearance at two hours. The conventional method is quantitative, whereas the bronchoscintigraphic method is semiquantitative. When the effects of terbutaline and placebo in the healthy subjects were compared both methods showed a significant increase in mucociliary clearance regardless of the method of administration of terbutaline. The bronchoscintigraphic method, however, showed that the radioactivity from the central bronchi was cleared slightly faster when terbutaline was administered by a metered dose inhaler or by both inhalers than by a dry powder inhaler alone. This information was not available with the conventional method, suggesting that the bronchoscintigraphic method may provide additional data not easily obtained by the conventional method.

When administered by a metered dose inhaler 1 mg of terbutaline doubled mucociliary clearance in both asthmatic and healthy subjects. This is consistent with previous findings in healthy subjects,[6-14] but contrasts with some previous observations in asthmatic subjects.[8 15 21] Generally, no effect has been seen after doses of β_2 agonists corresponding to 1 mg of terbutaline or less, whereas higher doses have caused some stimulation of mucociliary clearance. Our controlled study showed a clear stimulatory effect of only 1 mg of inhaled terbutaline on mucociliary clearance in asthmatic patients.

The asthmatic subjects were asymptomatic at the time of examination, so it was not surprising that mucociliary clearance on the day that placebo was given was similar in the asthmatic and the control subjects as reported in some,[17 19 20 31] but not all,[1 2 8 32] earlier studies.

In conclusion, we have shown that inhalation of 1 mg of terbutaline from a metered dose inhaler increased mucociliary clearance significantly in asthmatic patients and healthy subjects. When the same dose was inhaled from a dry powder inhaler the increase in mucociliary clearance was smaller, despite similar bronchodilatation, and was significantly above placebo values only in healthy subjects. The smaller effect of terbutaline given by dry powder inhaler on mucociliary clearance, while having similar effects on the FEV_1, is not fully understood. It may partly relate to different deposition patterns of terbutaline with the two devices.

A change in prescription from a metered dose inhaler to powder terbutaline in asthmatic subjects may be acceptable in terms of the effect on bronchodilatation, but an additional effect on mucociliary clearance may not be obtained with the dry powder formulation.

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