Response to aerosol salbutamol, SCH 1000, and placebo in cystic fibrosis

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ABSTRACT The responses of 20 patients with cystic fibrosis to a B₂ agonist, salbutamol, to an anticholinergic agent, SCH 1000, and to a placebo containing difluorodichloroethane and soya lecithin delivered by metered aerosol were compared. Flow rates decreased significantly after placebo ($p < 0.05$). FEV₁ increased significantly after salbutamol ($p < 0.05$), but the degree of these changes was small. There was a small but significant increase in FVC but no change in flow rates after SCH 1000. Specific conductance increased significantly ($p < 0.01$) after both salbutamol and SCH 1000. Thoracic gas volume remained unchanged with both drugs and placebo. Four of 20 patients had a clinically significant increase in flow rates with SCH 1000 and three with salbutamol. The consistent increases in sGaw coupled with minimal changes in flow rates, suggest that the physiological effects of both agents is to increase the compressibility of the airway. The results after placebo demonstrate the increased airway reactivity to irritants in cystic fibrosis. In view of this, attention should be paid to the possible irritant effects of inhaled medications.

Bronchodilators are often part of the treatment regimen for cystic fibrosis. Patients with this disease demonstrate bronchial hyperreactivity¹ but their response to bronchodilators is unclear. Data on their usefulness have been conflicting predominantly because of the paucity of controlled studies and the different pulmonary function parameters that have been used for evaluation. In one controlled study, Lifshitz and Denning² found that isoprenaline had a beneficial effect in some patients with cystic fibrosis. In uncontrolled studies some patients were found to have decreased expiratory flow rates after inhalation of isoprenaline.^{3,4}

The use of longer acting and more selective bronchodilators than isoprenaline has recently become widespread in asthma, but their use in cystic fibrosis has not been evaluated. Results with atropine in cystic fibrosis show a decrease in the pulmonary function abnormality, but side effects prohibit its clinical use.⁵

A controlled study was undertaken to assess the bronchodilator effects of a selective B₂ agonist, salbutamol, and an anticholinergic agent, SCH 1000 (ipratropium bromide) in cystic fibrosis. Salbutamol

has minimal effects on the cardiovascular system and a duration of action of four to six hours.⁶ SCH 1000 is an anticholinergic agent with minimal effects on bronchial secretions or on the cardiovascular system.⁷ It has been used in patients with chronic bronchitis and its bronchodilator effect is better than or comparable to that of a sympathomimetic.^{8,9} It has also been used as a bronchodilator in asthmatics.¹⁰

Methods

Twenty patients with cystic fibrosis (11 males and nine females) were studied. Informed consent to participate in the study was obtained from all subjects (and their parents in the case of minors). They were selected at random from the clinic population and represented a wide variation in clinical severity. They were all experienced in performing the pulmonary function tests in our laboratory so that neither a large intra-patient variability nor a learning effect was expected. The mean age and SD was 14.0 ± 3.71 (range 9 to 22 years). Ten patients had history of wheezing, one had hay fever, and one had a family history of asthma. Fourteen patients had positive skin tests to one or more allergens.

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FVC, the FEV₁, and the FEF_{25-75%} were obtained using a Collins nine litre water-filled spirometer. The thoracic gas volume (TGV) at functional residual capacity and airways resistance were measured using a variable pressure body plethysmograph by the techniques described by Dubois *et al.*¹¹ Specific airway conductance was determined from the reciprocal of airway resistance and the simultaneously determined thoracic gas volume. Peak expiratory flow rate was obtained with a Wright's peak flow meter.

The patients were studied in a single-blind manner on two or three separate days. The order of administration of the SCH 1000 and salbutamol was random. If two studies were done on the same day, the first medication was a placebo. In those patients, the SCH 1000 or salbutamol was given after the baseline was re-established or a minimum of four hours later, whichever time was greater. Bronchodilators were omitted for at least eight hours before each study. After measurements of FVC, FEV₁, FEF_{25-75%}, sGaw, and PFR, the patients inhaled either two puffs of placebo, 40 µg (two puffs) of SCH 1000, or 200 µg (two puffs) of salbutamol. These doses were delivered by a metered-dose inhaler which contained difluorodichloroethane as the main inert propellant, and soya lecithin as the surfactant. After inhalation, the FVC, FEV₁, and FEF_{25-75%} were repeated at 15 and 30 minutes. The FEF_{25-75%} post-bronchodilator was calculated using the pre-bronchodilator FVC so that comparisons were made at the same lung volume. The sGaw and PFR were repeated only at 30 minutes.

The doses chosen for bronchodilators have been previously reported to be effective in patients with asthma¹² and bronchitis.⁸ The 30-minute duration of assessment was used because both salbutamol and SCH 1000 achieve their peak effect within this time.⁹

A paired *t* test was used for analysis of the response to bronchodilators. An unpaired *t* test was used to assess difference in baseline pulmonary function.

Results

The mean baseline percent predicted FVC, FEV₁, and FEF_{25-75%} are shown in table 1. The range for baseline FEV₁ was 32% to 87% predicted and for the baseline FEF_{25-75%}, it was 15% to 86% predicted. The response to bronchodilator was assessed by calculating the percentage change from baseline.

Table 1 shows the results after inhalation of placebo, SCH 1000, and salbutamol for the duration of the study period. Pulmonary function was similar at the beginning of each drug trial. Forced vital capacity increased after both SCH 1000 and

Table 1 Percentage predicted FVC, FEV₁, and FEF_{25-75%}, and the difference from baseline after the drug indicated (mean ± 1 SE)

Time (min)	Drug	FVC (% predicted)			
		0	5	15	30
	Placebo	76.8 ± 3.8	-0.6 ± 1.0	-1.2 ± 1.1	-2.2 ± 1.4
	SCH 1000	76.2 ± 3.7	1.0 ± 0.8	1.7 ± 0.8*	2.0 ± 0.9*
	Salbutamol	77.6 ± 3.7	1.4 ± 0.6*	2.2 ± 0.9*	1.8 ± 1.0
Time (min)	Drug	FEV ₁ (% predicted)			
		0	5	15	30
	Placebo	62.4 ± 3.8	-0.7 ± 0.7	-2.7 ± 1.2*	-3.2 ± 1.3*
	SCH 1000	61.2 ± 3.7	0.0 ± 0.8	1.4 ± 0.8	1.0 ± 0.9
	Salbutamol	62.1 ± 3.9	-0.5 ± 1.2	2.8 ± 0.8†	2.1 ± 1.0*
Time (min)	Drug	FEF _{25-75%} (% predicted)			
		0	5	15	30
	Placebo	41.0 ± 4.8	-2.6 ± 1.5	-4.1 ± 2.4	-7.6 ± 3.2*
	SCH 1000	38.8 ± 4.8	-1.0 ± 1.9	-4 ± 1.3	1.8 ± 1.7
	Salbutamol	40.4 ± 5.1	2.4 ± 1.3	5.8 ± 1.7†	2.4 ± 2.1

* *p* < 0.05

† *p* < 0.01

salbutamol (*p* < 0.05). This increase was apparent at five minutes for salbutamol and at 15 minutes for SCH 1000. These changes in FVC were statistically significant although relatively small.

Fifteen minutes after inhalation of placebo aerosol flow rates decreased (*p* < 0.05). There was a significant increase in FEV₁ and FEF_{25-75%} (*p* < 0.05) by 15 minutes after salbutamol, but the response diminished by 30 minutes. There were no significant changes in flow rates after inhalation of SCH 1000.

Based on the response to bronchodilators and bronchoconstrictors in normal individuals using various parameters of pulmonary function, a change of clinical importance was determined to be 10% for FEV₁ and 25% for FEF_{25-75%}.^{13 14} Four of the 20 patients (20%) had a reduction of this degree in either the FEV₁ or the FEF_{25-75%} after the placebo. Two patients had these reductions in flow after SCH 1000 and one patient after salbutamol. Four of 20 (20%) had these increases after SCH 1000 and three of 20 (15%) after salbutamol. Only one subject had these increases to both SCH 1000 and salbutamol.

The effects of the drugs on TGV and PFR are shown in table 2. Thoracic gas volume remained unchanged with all three drugs. Peak expiratory flow increased significantly with SCH 1000 (*p* < 0.05) and salbutamol (*p* < 0.01), but not with placebo.

Specific airway conductance increased with both salbutamol and SCH 1000 (*p* < 0.01) but remained unchanged with placebo (figure).

Age, sex, baseline pulmonary function, and presence of skin test hypersensitivity did not correlate with the response to bronchodilators.

Side effects were minimal with both SCH 1000

Table 2 Mean $\pm$ SE peak flow rate (PFR) and thoracic gas volume (TGV) for 20 patients before and after drug indicated

PFR (litre/min)	Placebo	SCH 1000	Salbutamol
Baseline	314.1 $\pm$ 18.3	300.3 $\pm$ 14.3	322.9 $\pm$ 17.8
30 min	312.7 $\pm$ 18.3	319.1 $\pm$ 13.1	341.7 $\pm$ 17.3
	NS	p < 0.05	p < 0.001
TGV (litres)			
Baseline	2.33 $\pm$ 0.15	2.39 $\pm$ 0.17	2.31 $\pm$ 0.19
30 min	2.28 $\pm$ 0.17	2.28 $\pm$ 0.16	2.24 $\pm$ 0.16
	NS	NS	NS

NS — not significant

and salbutamol. Mean heart rate before salbutamol was 91.2 beats/min and this increased to 96.0 beats/min after the inhalation ($p < 0.05$). With SCH 1000 heart rate increased from a pre-treatment rate of 92.0/min to 93.1 after treatment (not significant). The mean heart rate before and after placebo remained at 92.1 beats per minute. Dryness of the mouth was reported only on specific enquiry in one subject with SCH 1000.

Discussion

Both salbutamol and SCH 1000 caused significant changes in the patients with cystic fibrosis but the pattern of bronchodilation differed strikingly from that seen in asthmatics. Specific airway conductance increased consistently but forced expiratory flow usually remained unchanged and in several instances actually decreased. This pattern has been observed in normal subjects after bronchodilators.^{15 16} Decreased flows after bronchodilators have been reported in uncontrolled studies in some patients with cystic fibrosis but not in conjunction with increased conductance.^{3 4}

Since sGaw increased consistently and is determined primarily by the diameters of central airways¹⁷ it is possible that the drugs had selective effects on the central airways. Our patients had varying degrees

of peripheral airway obstruction which would favour deposition of the aerosol in central airways. This may partly explain the consistent increase in sGaw but does not explain the decrease in forced expiratory flow observed in some patients. Furthermore, if the precise site of aerosol deposition were critical, those with mild disease should have had an increase in conductance and flow rates whereas those with severe disease only an increase in conductance. This pattern was not observed.

Studies of lung mechanics have explained certain characteristics of pulmonary function tests in patients with cystic fibrosis. Peak expiratory flow rates and maximum voluntary ventilation may be nearly normal in the face of severe airway obstruction and expiratory iso-volume flow-pressure curves show a remarkable preservation of effort dependent flow at high lung volumes.¹⁸ Further studies have suggested that these findings are the result of compression of gas in ectatic central airways rather than the preservation of normal lung units.¹⁹

Compressibility of airways is a determinant of maximum expiratory flow. According to theory of flow limitation advanced by Pride *et al*,²⁰ the reductions in maximum expiratory flow after bronchodilators in some of our patients may be caused by decrease in peripheral airways conductance, decrease in lung recoil, or increase in the critical transmural pressure at which dynamic compression of airways occurs. It is unlikely that the bronchodilators decreased peripheral airways conductance. Isoprenaline in large doses has been shown to reduce lung recoil,¹⁵ but not in smaller doses.¹⁶ Atropine given intravenously can also decrease lung recoil.²¹ In our study the inhaled doses of the beta-adenergic and the anticholinergic bronchodilators were small and it is unlikely a decrease in lung recoil is the explanation for the reduced or unchanged flow rates.

Bronchodilators increase compliance of airways²² and this would increase the tendency for dynamic compression which would reduce maximum expiratory flow. The variability of our results for maximal expiratory flow which increased, decreased, or remained unchanged after the bronchodilators, probably represents the opposing effects of decrease in airway resistance and increase in airway collapsibility.

The significant reduction in flow rates after placebo containing propellant and lubricant has not been reported previously in cystic fibrosis. Difluoro-dichloroethane and soya lecithin have been shown to decrease specific conductance and flow rates in some asthmatics but not in normal subjects.^{23 24} This same observation in patients with cystic fibrosis may be related to heightened bronchial reactivity to irritants that has been demonstrated in this disease.²⁵ The relative contribution of the propellant and surfactant to the bronchoconstriction is unknown. Despite flow rates being reduced after placebo, sGaw did not change significantly. The explanation for this observation is unclear. It may indicate a negligible effect of irritants on ectatic large airways. The possibility remains that the reduction in flow rates results from the effect of forced expiratory mechanical manoeuvres on ectatic airways. However, if it were solely a mechanical effect, similar changes should have been observed after SCH 1000 and salbutamol.

Bronchodilators in cystic fibrosis must be evaluated from their clinical effect rather than their statistical significance. Statistically, salbutamol causes greater improvement in flow rates than SCH 1000 but the beneficial effect of both is small in terms of clinical improvement in most patients. The percentage changes from baseline were greater with the FEF₂₅₋₇₅% than with the FEV₁. This points out that large percentage changes are not synonymous with statistical or clinical significance of the test when determining a response to bronchodilators. In addition, using sGaw or PFR as the only parameters for assessment may be misleading because they may simply be reflecting an effect on large ectatic airways.

The small responses observed are comparable to previous studies using isoprenaline in cystic fibrosis.^{2 3 26} When bronchoconstriction is induced with methacholine in patients with cystic fibrosis the response to salbutamol is slower and less complete than in asthmatics.¹ Nevertheless, in those patients demonstrating a response, SCH 1000 and salbutamol might be preferable to isoprenaline because of fewer side effects and longer duration of action.

Whether or not anticholinergic agents delivered by a different method would be more useful than a

B-agonist cannot be answered by this study. Nevertheless, the response to SCH 1000 would suggest that some patients have increased vagal tone which is in agreement with observations using atropine in patients with cystic fibrosis.⁵

The treatment regimen in cystic fibrosis includes many drugs. In view of the heightened bronchial reactivity that some patients demonstrated to the propellant and surfactant, attention should be paid to the possibility of detrimental effects on the airways from other medications caused by their method of delivery and their chemical and physical properties. Furthermore, in studies assessing response of cystic fibrosis patients to inhaled medications, the importance of airway irritability to placebo should be assessed.

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