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Effect of salbutamol and ipratropium bromide on airway calibre and bronchial reactivity in asthma and chronic bronchitis

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ABSTRACT: Bronchial reactivity to agonists such as histamine is seen in both chronic bronchitis and asthma, two conditions with different pathological changes in the airways. Salbutamol, when given acutely, reduces bronchial reactivity in patients with asthma, but the mechanism has not been clarified. To determine whether the effect of salbutamol depends on the pathological changes underlying the increased reactivity, we have compared the effect of salbutamol and ipratropium on bronchial reactivity in nine patients with asthma and ten with chronic bronchitis. Each drug was given on separate days in increasing doses (5, 100, 750, 1,000 μg) according to a double-blind, randomized design. Changes in forced expiratory volume in one second (FEV_1) and specific airways conductance (sGaw) were measured after each dose, and the provocative concentration of histamine causing a 20% fall in the FEV_1 (PD_{20}) was determined after the last dose. Salbutamol and ipratropium were equipotent in the asthmatic subjects and caused a similar maximal increase in FEV_1 (0.58 and 0.57 *l*) and sGaw (0.166 and 0.154 $s^{-1} \cdot kPa^{-1}$). The two drugs also produced similar changes in the patients with chronic bronchitis, although the maximum response to both drugs was smaller (FEV_1 0.29 and 0.32 *l*; sGaw 0.056 and 0.060 $s^{-1} \cdot kPa^{-1}$; $p<0.05$). Despite differences in bronchodilatation the increase in histamine PD_{20} following salbutamol was similar in the asthmatic and bronchitic subjects (2.26 and 1.90 doubling doses (DD)) and greater in both groups ($p<0.05$) than the change in PD_{20} with ipratropium (0.84 and 0.56 DD). These data show that salbutamol causes a greater reduction in bronchial reactivity than ipratropium in patients with asthma and chronic bronchitis, and that both drugs have a similar effect in the two conditions, despite differences in the underlying pathology and despite the greater bronchodilatation observed in asthmatic patients.

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Bronchial reactivity is increased in most patients with asthma [1, 2] and in many patients with chronic bronchitis and airflow obstruction [3–11]. The pathological changes seen in the airways in the two conditions are clearly different and it is likely that the mechanisms underlying bronchial hyperreactivity are also different, as discussed elsewhere [12]. The clinical importance of hyperreactivity may also differ in the two conditions. When given as a single dose to patients with asthma, $beta_2$-agonists cause a marked reduction in the airway response to agonists such as histamine [13–19]. The mechanism underlying this effect is not understood but does not appear to be directly due to bronchodilatation since ipratropium bromide causes a much smaller reduction in bronchial reactivity than salbutamol for the same degree of bronchodilatation [14, 15, 20]. There is evidence to suggest that in chronic bronchitis bronchial reactivity is more dependent on airway calibre than it is in asthma [6, 10] and, if this is true, agents that produced similar bronchodilatation in subjects with chronic bronchitis should produce similar effects on bronchial reactivity. An alternative view is that the effect of $beta_2$-agonists on bronchial reactivity is due to a direct action on airway smooth muscle. If this is correct beta-agonists would be expected to have the same effect on bronchial reactivity measurements irrespective of underlying pathological mechanisms, and would be expected to reduce bronchial reactivity more than ipratropium in both chronic bronchitis and in asthma.

We have therefore studied the effect of salbutamol on bronchial reactivity in patients with asthma and chronic bronchitis, comparing the response to salbutamol with

that to ipratropium bromide. The study also enabled us to compare the potency of salbutamol and ipratropium as bronchodilators: many studies have suggested that ipratropium bromide is more effective in chronic bronchitis than it is in asthma, but these studies have usually compared single doses of the two drugs [21–24] that are not necessarily equipotent [20].

Methods

Subjects

Ten subjects with asthma and 10 with chronic bronchitis were recruited. At an initial screening test the asthmatic subjects were required to be nonsmokers, with a forced expiratory volume in one second (FEV_1) of 70% predicted or greater, and a provocative dose of histamine causing a 20% fall in FEV_1 (PD_{20}) of 2 μmol or less. Subjects with chronic bronchitis all fulfilled the MRC definition of chronic bronchitis, had a PD_{20} of 4 μmol or less, and an FEV_1 of at least 1 *l*. Subjects were excluded from both groups if taking treatment other than a beta-agonist, anti-muscarinic agent or steroid by inhalation.

Measurement of airway calibre

FEV_1 was measured with a dry bellows spirometer (Vitalograph, Buckingham), using the highest of two successive readings within 5% of each other. Specific airways conductance (sGaw) was measured with the subject panting in a body plethysmograph on line to a microprocessor (Gould 2800, Dayton, Ohio), and calculated as the mean of three satisfactory measurements, each consisting of three panting breaths.

Histamine challenge test

Histamine challenge tests were performed by the method of YAN *et al.* [25] using De Vilbiss No. 40 nebulizers which had been shown by prior testing to have an output in the range 0.0025–0.0035 ml per actuation. After resting for 10 min baseline FEV_1 and forced vital capacity (FVC) were measured. Three puffs of normal saline were then administered followed by increasing doses of histamine, starting with 0.03 μmol and continuing with doubling increments. FEV_1 was recorded one minute after each dose as the best of two consecutive readings within 100 ml of each other, and was followed immediately by the next dose of histamine. The test was stopped when the FEV_1 had fallen by 20% from post-saline values, or when a dose of 8 μmol histamine had been given.

Bronchodilator dose-response studies

Salbutamol and ipratropium bromide were given in sequential doses of 5, 100, 750 and 1,000 μg at 20 min intervals. FEV_1 and sGaw were measured 20 min after each dose and followed immediately by the next dose. The drugs were delivered by Inspiron nebulizer driven by 7 $l \cdot min^{-1}$ of air until all the drug had been nebulized. Both drugs were diluted with normal saline so that identical doses (in mg) of the two drugs were nebulized over the same period of time.

Study design

Dose-response studies with salbutamol and ipratropium bromide were carried out in random order and double-blind fashion. After a preliminary visit to establish that the entry criteria were fulfilled, subjects were asked to attend on two further occasions, at the same time each day, and not to take their bronchodilator inhalers for 8 h prior to either visit. After resting for 10 min baseline FEV_1 and sGaw were measured followed by a histamine challenge test. FEV_1 was then measured at 5 min intervals until it had returned to within 95% of baseline; the bronchodilator dose response study was then carried out. A histamine challenge test was performed 20 min after the last dose of drug.

The study was approved by the Nottingham City Hospital Ethics Committee. All patients gave informed written consent.

Analysis

The PD_{20} was calculated by linear interpolation. Extrapolation was allowed up to one doubling dose above the maximum histamine dose (up to 16 μmol), but was only necessary in two instances. Two subjects who did not have a 20% fall in FEV_1 with the highest post-salbutamol dose of histamine even after extrapolation were allotted a value of 16 μmol. Geometric mean values of PD_{20} were used in all calculations.

The difference between baseline and final PD_{20} values was expressed in doubling doses of histamine for each subject. Change in PD_{20}, FEV_1 and sGaw following salbutamol and ipratropium were compared within the asthmatic and chronic bronchitic groups by paired Student's t-test, and between subject groups by unpaired t-tests.

Results

One asthmatic subject failed to complete the full study. The results from nine asthmatic subjects (4 male, 5 female) aged 19–49 yrs and ten chronic bronchitic subjects (all male) aged 58–81 yrs were therefore analysed. The subjects' regular treatment, smoking histories, and results of skin tests are shown in tables 1 and 2.

Baseline FEV_1, sGaw and PD_{20} values are shown in tables 1 and 2. There were no significant differences between baseline values of these measurements on the salbutamol and ipratropium study days in either group.

Table 1. – Baseline FEV_1, sGaw and PD_{20} measurements, atopic status, smoking history, and regular treatment in the subjects with asthma

		FEV_1		sGaw	PD_{20}	Atopic status	Smoking history	Treatment
		l	(% pred)	$s^{-1}\cdot kPa^{-1}$	μmol			
1	S	3.15	(106)	0.094	0.85	Atopic	NS	Salbutamol
	I	3.05	(103)	0.099	1.80			
2	S	3.90	(100)	0.110	0.80	Not	NS	Salbutamol
	I	3.95	(101)	0.110	0.34	tested		Beclomethasone
3	S	2.90	(94)	0.203	0.38	Atopic	NS	Salbutamol
	I	2.75	(89)	0.170	0.38			
4	S	2.15	(77)	0.024	0.95	Atopic	NS	Salbutamol
	I	2.15	(77)	0.020	0.09			Beclomethasone
5	S	3.55	(108)	0.117	0.50	Non-	ES	Salbutamol
	I	3.35	(102)	0.147	0.24	atopic		
6	S	1.30	(51)	0.026	0.48	atopic	NS	Salbutamol
	I	1.50	(55)	0.018	0.07			
7	S	3.25	(97)	0.130	1.60	Non-	NS	Fenoterol
	I	3.50	(104)	0.150	2.40	Atopic		Beclomethasone
8	S	2.50	(104)	0.161	1.40	Atopic	NS	Terbutaline
	I	2.40	(100)	0.127	1.25			Budesonide
9	S	2.80	(76)	0.103	0.23	Atopic	NS	Salbutamol
	I	2.70	(73)	0.108	0.32			

FEV_1: forced expiratory volume in one second; sGaw: specific airways conductance; PD_{20}: provocative dose producing a 20% fall in FEV_1; NS: nonsmoker; ES: ex-smoker; S: salbutamol study day; I: ipratropium

Table 2. – Baseline FEV_1, sGaw and PD_{20} measurements, atopic status, smoking history, and regular treatment in the subjects with chronic bronchitis

		FEV_1		sGaw	PD_{20}	Atopic status	Smoking history	Treatment
		l	(% pred)	$s^{-1}\cdot kPa^{-1}$	μmol			
1	S	1.30	(58)	0.033	0.65	Not	ES	Salbutamol
	I	1.25	(55)	0.051	0.27	tested		Beclomethasone
2	S	1.25	(43)	0.015	1.50	Non-	ES	Salbutamol
	I	1.20	(41)	0.031	0.25	atopic		Ipratropium
3	S	1.20	(41)	0.020	2.80	Non-	S	Salbutamol
	I	1.20	(41)	0.025	1.80	atopic		Ipratropium
4	S	1.90	(65)	0.117	0.38	Atopic	ES	Salbutamol
	I	1.95	(67)	0.063	0.58			Ipratropium
5	S	1.70	(70)	0.132	0.48	Not	ES	Salbutamol
	I	1.45	(60)	0.126	0.08	tested		
6	S	3.20	(100)	0.057	4.20	Non-	S	
	I	3.05	(95)	0.068	4.00	atopic		
7	S	2.00	(62)	0.043	3.40	Non-	S	
	I	1.95	(60)	0.034	6.50	atopic		
8	S	1.10	(38)	0.050	0.65	Non-	ES	Salbutamol
	I	0.85	(29)	0.060	1.00	atopic		
9	S	1.00	(33)	0.040	0.04	Non-	S	Salbutamol
	I	1.10	(37)	0.031	0.21	atopic		Ipratropium
10	S	1.20	(58)	0.025	0.05	Non-	ES	Salbutamol
	I	1.30	(63)	0.019	0.08	atopic		

For meanings of abbreviations see legend to table 1.

Change in FEV_1 and sGaw with salbutamol and ipratropium bromide

Following the initial histamine challenge test FEV_1 had returned to 95% of baseline within 1 h in all subjects. There was a mean maximum increase in FEV_1 of 0.58 *l* in the asthmatic subjects and 0.29 *l* in the chronic bronchitic subjects following salbutamol compared to 0.57 *l*, and 0.32 *l*, respectively following ipratropium. The differences between the asthmatic and chronic bronchitic subjects were significant with both drugs for both FEV_1 ($p<0.05$) and sGaw (0.166 *vs* 0.056 $s^{-1}\cdot kPa^{-1}$ for salbutamol, 0.154 vs 0.060 $s^{-1}\cdot kPa^{-1}$ for ipratropium, $p<0.01$ for both drugs). The changes in FEV_1 and sGaw following salbutamol and ipratropium did not differ significantly in the subjects with asthma, or in those with chronic bronchitis (fig. 1).

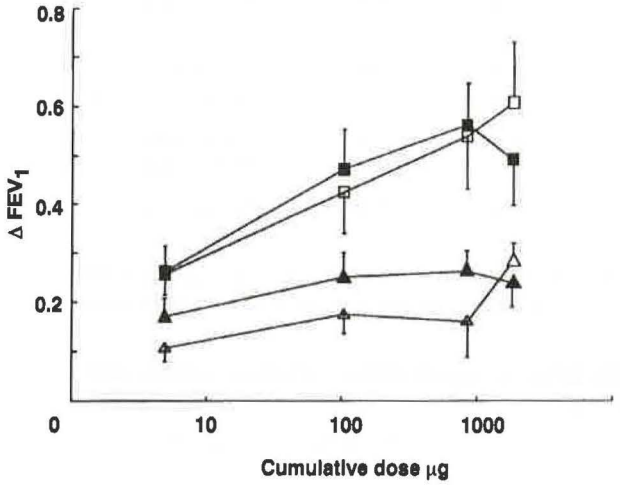

Fig. 1. – Mean (SE) change in FEV_1 (*l*) with cumulative doses of salbutamol (open symbols) and ipratropium (closed symbols) in subjects with asthma (square symbols) and chronic bronchitis (triangles). FEV_1: forced expiratory volume in one second.

Changes in PD_{20} with salbutamol and ipratropium bromide

In the asthmatic subjects mean PD_{20} changed from 0.80 μmol to 4.75 μmol following salbutamol and from 0.67 μmol to 1.06 μmol following ipratropium bromide. The mean increase in PD_{20} was significantly higher with salbutamol than with ipratropium (2.26 *vs* 0.84 doubling doses, $p<0.05$).

In the subjects with chronic bronchitis the mean PD_{20} values changed from 1.41 μmol to 4.52 μmol following salbutamol and from 1.48 μmol to 2.40 μmol following ipratropium bromide. The difference in the change in PD_{20} between salbutamol and ipratropium (1.90 *vs* 0.56 DD) was significant (fig. 2, $p<0.05$). The change in PD_{20} with salbutamol was similar in the asthmatic and chronic bronchitic subjects. Ipratropium bromide also caused a similar change in PD_{20} in the two groups. Change in PD_{20} did not correlate with change in airway calibre following either drug in either group of subjects.

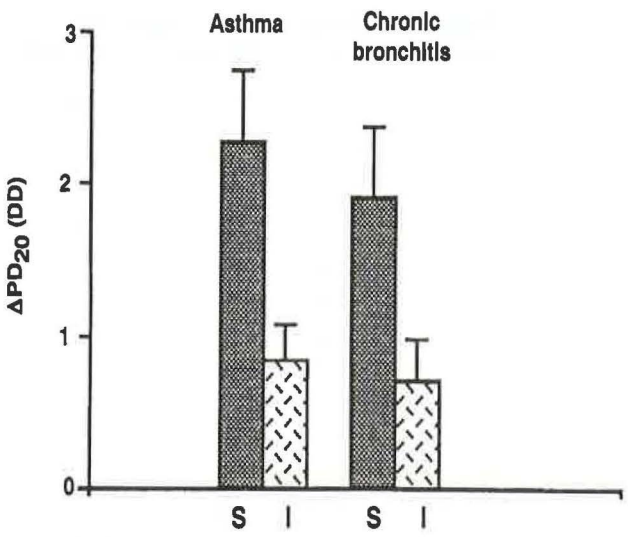

Fig. 2. – Increase in PD_{20} (in doubling doses of histamine) after salbutamol (S) and ipratropium bromide (I) in subjects with asthma and chronic bronchitis. PD_{20}: provocative dose producing a 20% fall in forced expiratory volume in one second.

Discussion

In this study both salbutamol and ipratropium bromide in cumulative doses up to 1,855 μg caused dose-related bronchodilatation in subjects with asthma and in subjects with chronic bronchitis. We studied patients with relatively mild asthma and chronic bronchitis because we wished to carry out histamine challenge tests. The relative effect of the two drugs may be different in subjects with more severe disease but this seems unlikely and we know of no evidence to suggest that this is the case. The regular medication taken by subjects was not changed during the study and should not have influenced the within subject comparisons that we made. Corticosteroids have been shown not to alter the bronchodilator response to $beta_2$-agonists or ipratropium in patients with mild asthma [26, 27].

One of the principal aims of this study was to compare the bronchodilator potency of salbutamol and ipratropium. Both drugs produced greater bronchodilatation in the subjects with asthma than in those with chronic bronchitis. There was no significant difference between salbutamol and ipratropium in the bronchodilatation achieved in the asthmatic subjects for a given dose, showing, as in our previous smaller study [20] that the two drugs are roughly equipotent. We are less confident that the drugs were equipotent in the chronic bronchitic subjects because the bronchodilatation in these subjects was small. Previous studies have suggested that, whereas beta-agonists are more effective bronchodilators than anti-muscarinic agents in asthmatic subjects, there is less difference between the drugs in chronic bronchitis [21–23], and some indication that antimuscarinic agents might be more effective [28]. In all of these studies however the drugs were compared in single doses so that it was not possible to assess potency. We are unaware of any previous dose-response

comparison of the two drugs in subjects with chronic bronchitis.

Although the two drugs were equipotent in the asthmatic patients we cannot draw final conclusions about their relative efficacy without giving higher doses to be sure that maximum bronchodilatation had been achieved. Higher doses of salbutamol have produced greater bronchodilatation in some studies of subjects with more severe chronic bronchitis [29, 30], but with the currently available formulations it would be difficult to give a higher dose of ipratropium.

A reduction in bronchial responsiveness to histamine and methacholine has been seen in several studies following the acute administration of beta$_2$-agonists, the magnitude usually being between 2 and 4 doubling doses of agonist [31]: the maximum reported change in PD_{20} with ipratropium bromide has been 1.4 doubling doses [14] and most workers have found a change of one doubling dose or less [15, 20, 32].

Change in airway calibre may itself affect the measurement of bronchial reactivity [33] and this may account for the small increase in PD_{20} observed with ipratropium bromide. The change with salbutamol, however, appears to be due mainly to an additional effect of the drug since it caused a much larger change in PD_{20} than ipratropium in both groups of patients despite producing the same degree of bronchodilatation. Salbutamol might exert its effect on bronchial reactivity in several ways; by reducing mediator release from inflammatory cells [35], through a direct effect on smooth muscle [36] and possibly by reducing vascular leakage and oedema formation [37].

There are reasons to assume that the mechanisms underlying heightened bronchial reactivity are different in chronic bronchitis and asthma. PD_{20} measurements show a closer relationship to FEV_1 in chronic bronchitis than in asthma, and for any given FEV_1 subjects with chronic bronchitis tend to show less bronchial reactivity than those with asthma [6, 10]. The nature of the relationship between airway calibre and bronchial reactivity in chronic bronchitis is still debated, but the role of inflammation in causing the increase in reactivity appears to be small [12, 35]. If salbutamol was reducing bronchial reactivity by reducing mediator release or vascular leakage the effects of salbutamol on bronchial reactivity would be expected to differ in chronic bronchitis and asthma. Since salbutamol and ipratropium produced very similar changes in PD_{20} values in the two groups of patients it appears that their effects are unrelated to the known differences in airway pathology in the two disease states. The acute effects of salbutamol on airway reactivity are therefore most likely to be due predominantly to a direct effect of salbutamol on airway smooth muscle.

Thus, this study suggests that despite differences in the pathological changes in the airways in asthma and chronic bronchitis the effects of salbutamol and of ipratropium bromide on bronchial reactivity are similar in the two conditions, with salbutamol having a greater effect on reactivity than ipratropium in both. Salbutamol and ipratropium appear to be equipotent bronchodilators; the response to both drugs was greater in subjects with asthma than in those with chronic bronchitis.

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L'effet du salbutamol et du bromure d'ipratropium sur le calibre des voies aériennes et sur la réactivité bronchique dans l'asthme et la bronchite chronique. B.G. Higgins, R. M. Powell, S. Cooper, A.E. Tattersfield.

RÉSUMÉ: La réactivité bronchique à l'égard d'agonistes du type histamine existe à la fois dans la bronchite chronique et dans l'asthme, deux affections dont les lésions anatomopathologiques des voies aériennes sont différentes. Le salbutamol en administration aiguë réduit la réactivité bronchique chez les patients asthmatiques mais le mécanisme de cette action n'a pas été éclairci. Pour l'investiguer davantage et pour déterminer si l'effet du salbutamol est lié aux lésions anatomiques qui sont sous-jacentes à l'augmentation de réactivité, nous avons comparé l'effet du salbutamol et de l'ipratropium sur la réactivité bronchique chez neufs sujets atteints d'asthme et dix atteints de bronchite chronique. Chaque médicament a été administré à des jours séparés, à des doses croissantes (5, 100, 750, 1000 μg) selon un shéma randomisé en double aveugle. Les modifications du VEMS et de la conductance spécifique des voies aériennes ont été mesurées après chaque dose de produit et la concentration d'histamine provoquant une chute de 20% du VEMS (PD_{20}), a été déterminée après la dernière dose. Le salbutamol et l'ipratropium sont équipotents chez les sujets asthmatiques et provoquent une augmentation maximale similaire du VEMS (0.58 et 0.57 *l*) et de la conductance spécifique (0.166 et 0.154 $s^{-1} \cdot kPa^{-1}$). Les deux médicaments ont produit également des modifications semblables chez les patients atteints de bronchite chronique, quoique la réponse maximale aux deux médicaments y soit plus faible que chez les asthmatiques (VEMS 0.29 et 0.32 *l*; sGaw 0.056 et 0.060 $s^{-1} \cdot kPa^{-1}$; $p<0.05$). Malgré les différences de bronchodilatation, l'augmentation du PD_{20} d'histamine après le salbutamol, est similaire chez les sujets asthmatiques et bronchitiques (doses de doublement (DD) de 2.26 et 1.90 respectivement). Elle s'avère dans les deux groupes ($p<0.05$) plus élevée que la modification de PD_{20} obtenue par l'ipratropium (0.84 et 0.56 DD). Ces données montrent que le salbutamol entraîne une réduction plus marquée de la réactivité bronchique que l'ipratropium chez les patients atteints d'asthme et de bronchite chronique mais que les deux médicaments ont un effet similaire dans les deux conditions malgré les différences de la pathologie sous-jacente et malgré une augmentation plus marquée de la bronchodilatation chez les sujets asthmatiques.
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