Dose related effects of salbutamol and ipratropium bromide on airway calibre and reactivity in subjects with asthma

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ABSTRACT The relationship between change in airway calibre and change in airway reactivity after administration of bronchodilator drugs has been investigated by comparing the effect of increasing doses of inhaled salbutamol and ipratropium bromide on the forced expiratory volume in one second (FEV₁), specific airways conductance (sGaw), and the dose of histamine causing a 20% fall in FEV₁ (PD₂₀) in six subjects with mild asthma. On each of 10 occasions measurements were made of baseline FEV₁, sGaw, and PD₂₀ after 15 minutes' rest, and followed one hour later, when the FEV₁ had returned to baseline, by a single nebulised dose of salbutamol (placebo, 5, 30, 200 and 1000 µg) or ipratropium (placebo, 5, 30, 200 and 1000 µg) given in random order. Measurements of FEV₁, sGaw and PD₂₀ were repeated 15 minutes after salbutamol and 40 minutes after ipratropium. Salbutamol and ipratropium caused a similar dose related increase in FEV₁ and sGaw, with a mean increase after the highest doses of 0.76 and 0.69 litres for FEV₁ and 1.15 and 0.96 s⁻¹ kPa⁻¹ for sGaw. Salbutamol also caused a dose related increase in PD₂₀ to a maximum of 2.87 (95% confidence interval 2.18-3.55) doubling doses of histamine after the 1000 µg dose, but ipratropium bromide caused no significant change in PD₂₀ (maximum increase 0.24 doubling doses, 95% confidence interval -0.73 to 1.22). Thus bronchodilatation after salbutamol was associated with a significantly greater change in airway reactivity than a similar amount of bronchodilatation after ipratropium bromide. This study shows that the relation between change in airway reactivity and bronchodilatation is different for two drugs with different mechanisms of action, suggesting that change in airway calibre is not a major determinant of change in airway reactivity with bronchodilator drugs.

Several studies have confirmed an association between increased airway reactivity and diminished airway calibre in subjects with airflow obstruction¹⁻⁸ but the cause of the association is not clear. There are reasons to expect that an increase in airway reactivity would lead to increased airflow obstruction, and vice versa that an increase in airflow obstruction would increase airway reactivity, by a combination of mechanisms.^{9,10} Alternatively, both airflow obstruction and increased airway reactivity may occur as a result of a common underlying disease process.

Bronchodilator drugs such as β agonists, antimuscarinic agents, and methylxanthines have been shown to cause a decrease in airway reactivity in conjunction

with bronchodilatation,¹¹⁻²¹ but whether different drugs cause a similar change in airway reactivity for a given change in airway calibre has not been investigated in dose-response studies. If airway calibre is a major determinant of airway reactivity a consistent relation might be expected between change in airway calibre and change in reactivity after the administration of bronchodilator drugs with different mechanisms of action. This study investigated this relation by measuring change in airway calibre and reactivity after increasing doses of salbutamol and ipratropium bromide in subjects with mild asthma.

Methods

SUBJECTS

We studied three men and three women with asthma aged 21-39 years, all non-smokers. All had mild

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stable asthma with a resting FEV₁ over 60% of the predicted value, an increase in FEV₁ of over 15% after 200 µg salbutamol administered by metered dose inhaler, and a provocative dose of histamine causing a 20% fall in FEV₁ (PD₂₀ FEV₁) of less than 1.8 µmol.²² Two subjects inhaled β agonists intermittently as required, four inhaled them regularly every day (maximum dose 800 µg daily), and two of these also inhaled steroids regularly. All treatment was withheld for eight hours before each study. The investigation was approved by the City Hospital ethics committee.

METHODS

FEV₁ was measured with a dry bellows spirometer (Vitalograph, Buckingham), the best of three attempts being accepted. Specific airways conductance (sGaw) was measured with the subject panting in a body plethysmograph (Fenyes and Gut, Basel, Switzerland) on line to a microprocessor, and calculated from the mean of six consecutive measurements, each measurement analysing three panting breaths.

Salbutamol and ipratropium bromide solutions for nebulisation were prepared immediately before each study by diluting stock solutions of salbutamol sulphate 5 mg/ml (Allen and Hanburys) and ipratropium bromide 0.25 mg/ml (Boehringer Ingelheim) with a 150 mM sodium chloride solution. Airway challenge tests were performed by the method of Yan *et al*²² to a maximum dose of 16 µmol of histamine. Inhalation of saline was followed by doubling doses of histamine from 0.03 µmol until there was a 20% fall in FEV₁ from the post-saline value. PD₂₀ was estimated by linear interpolation on a log dose-response plot.

PROCEDURE

Subjects were studied at the same time on 10 different

days, on which drug and placebo were administered according to a randomised protocol; this included four doses of ipratropium bromide plus ipratropium placebo (placebo I) and four doses of salbutamol plus salbutamol placebo (placebo S). The study was double blind, except that the operator was told that the procedure was either for salbutamol/placebo or for ipratropium/placebo so that measurements could be timed appropriately.

On each study day baseline FEV₁ and sGaw were measured after 15 minutes' rest and, provided that baseline FEV₁ was within 10% of that on day 1, the first histamine challenge test was carried out. The subject then rested for one hour before the FEV₁ and sGaw measurements were repeated. Salbutamol, ipratropium bromide, or 150 mM saline (placebo) solutions were then administered from an Inspiron nebuliser (Bard Ltd, Sunderland), which when driven by air at 8 litres/min emitted 4 ml of solution during eight minutes of tidal breathing. The nebuliser was primed with 5 ml of solution, at drug concentrations of 1.25, 7.5, 50, and 250 µg/ml, so that doses of 5, 30, 200, and 1000 µg of drug were nebulised. The same nebuliser was used for all studies on each subject. Measurements of sGaw, FEV₁, and PD₂₀ were repeated 15 minutes after the end of the salbutamol or the salbutamol placebo inhalation and 40 minutes after the ipratropium bromide or the ipratropium placebo inhalation.

DATA ANALYSIS

Change in FEV₁ and sGaw between the baseline value before the first histamine challenge and the post-drug value immediately before the second histamine challenge was calculated for each subject. Change in histamine PD₂₀ between the first and second histamine

Mean (SEM) FEV₁ (l) and sGaw (s⁻¹ kPa⁻¹) at baseline and before and after drug, geometric mean PD₂₀ (µmol) at baseline and after drug, and geometric mean (SEM) change in PD₂₀ (ΔPD₂₀) between baseline and after drug (doubling doses)

Dose (µg)	Baseline			Before drug		After drug			
	FEV ₁	sGaw	PD ₂₀	FEV ₁	sGaw	FEV ₁	sGaw	PD ₂₀	ΔPD ₂₀
SALBUTAMOL									
Placebo	3.10 (0.12)	0.61 (0.14)	0.387	3.15 (0.19)	0.66 (0.20)	2.98 (0.26)	0.60 (0.16)	0.305	-0.34 (0.38)
5	3.07 (0.13)	0.66 (0.14)	0.395	3.13 (0.15)	0.74 (0.20)	3.13 (0.15)	0.78 (0.16)	0.449	0.18 (0.16)
30	3.09 (0.13)	0.56 (0.06)	0.395	3.16 (0.19)	0.76 (0.19)	3.42 (0.20)	1.11 (0.19)	0.814	1.04 (0.15)
200	3.02 (0.12)	0.67 (0.12)	0.596	3.03 (0.18)	0.68 (0.13)	3.56 (0.21)	1.40 (0.23)	1.738	1.54 (0.51)
1000	3.00 (0.16)	0.62 (0.14)	0.490	3.12 (0.16)	0.71 (0.13)	3.76 (0.20)	1.77 (0.22)	3.570	2.87 (0.27)
IPRATROPIUM									
Placebo	3.11 (0.16)	0.68 (0.11)	0.696	3.21 (0.21)	0.71 (0.15)	3.26 (0.17)	0.91 (0.17)	0.608	-0.19 (0.25)
5	3.14 (0.14)	0.62 (0.11)	0.434	3.12 (0.14)	0.60 (0.10)	3.28 (0.18)	0.94 (0.04)	0.498	0.20 (0.45)
30	3.06 (0.16)	0.67 (0.10)	0.741	3.06 (0.19)	0.69 (0.12)	3.49 (0.21)	1.29 (0.17)	0.528	-0.47 (0.24)
200	3.03 (0.17)	0.61 (0.14)	0.600	2.98 (0.15)	0.58 (0.12)	3.51 (0.17)	1.32 (0.20)	0.749	0.32 (0.27)
1000	2.97 (0.16)	0.59 (0.12)	0.444	3.08 (0.14)	0.69 (0.14)	3.66 (0.24)	1.43 (0.20)	0.525	0.24 (0.38)
Mean	3.06 (0.05)	0.63 (0.04)	0.503	3.10 (0.07)	0.68 (0.06)				

sGaw—specific airways conductance; PD₂₀—dose of histamine causing a 20% fall in FEV₁.

Fig 1 Change in FEV_1 (litres) and specific airways conductance ($sGaw$, $s^{-1} kPa^{-1}$) with increasing dose (μg) of salbutamol (○—○) and ipratropium bromide (△—△).

tests was expressed in $\log_2$ (doubling dose) units.²³

Student's paired t test was used to compare baseline FEV_1 values with values one hour after the first histamine challenge, and to compare baseline FEV_1 , $sGaw$, and $\log PD_{20}$ values with measurements after the salbutamol and ipratropium placebo inhalations. Dose-response gradients for salbutamol and ipratropium bromide were calculated for FEV_1 , $sGaw$, and histamine PD_{20} by least squares regression. Log dose-response gradients for FEV_1 , $sGaw$, and $\log$ histamine PD_{20} , and the gradient of change in $\log PD_{20}$ with change in FEV_1 and $sGaw$, were compared between drugs within subjects by Student's t test. A p value of <0.05 was considered significant.

Results

The mean (SEM) FEV_1 at baseline and one hour after the first histamine challenge (pre-drug value) was 3.06 (0.05) and 3.10 (0.07) litres. Individual values for FEV_1 one hour after the histamine challenge were greater than 90% of baseline on all 60 study days. The mean $sGaw$ at baseline and one hour after the first challenge was 0.63 (0.04) and 0.68 (0.06) $s^{-1} kPa^{-1}$ respectively.

Neither of the two placebo inhalations caused a significant change in FEV_1 , $sGaw$, or PD_{20} (table). There was a linear increase in FEV_1 and $sGaw$ with increasing log dose of salbutamol and ipratropium bromide, which was similar and significant for both drugs ($p < 0.001$ and $p < 0.01$ for both indices after salbutamol and ipratropium bromide respectively: fig 1). There was a linear increase in $\log PD_{20}$ with increasing doses of salbutamol ($p < 0.001$) but not with ipratropium bromide ($p = 0.56$: fig 2), and this relationship was significantly different for the two drugs ($p < 0.05$). The mean increase in PD_{20} after the 1000 μg dose of salbutamol was 2.87 doubling doses (95% confidence interval 2.18 to 3.55) and after ipratropium bromide was 0.24 doubling doses (95% confidence interval -0.73 to 1.22). With salbutamol the increase in $\log PD_{20}$ was related to increase in FEV_1 and $sGaw$ ($p < 0.001$ for both indices), but there was no significant linear relation between change in $\log PD_{20}$ and either FEV_1 or $sGaw$ for ipratropium bromide ($p = 0.17$ and 0.83 : fig 3). The difference between the drugs in this respect was highly significant for both FEV_1 ($p < 0.01$) and $sGaw$ ($p < 0.001$).

Fig 2 Change in histamine PD_{20} (μmol) with increasing dose (μg) of salbutamol (○—○) and ipratropium bromide (△—△).

Fig 3 Relation of change in PD_{20} (μmol) to change in FEV_1 (litres) and $sGaw$ ($s^{-1} kPa^{-1}$) after salbutamol (○—○) and ipratropium bromide (△—△).

Discussion

Although a relation between airway reactivity and airway calibre is widely recognised it is still uncertain whether airway hyperreactivity causes bronchoconstriction, whether pre-existing bronchoconstriction causes airway hyperreactivity, or indeed whether both airway hyperreactivity and airflow obstruction are the result of a common underlying disease process. We have investigated the relation between airway calibre and airway reactivity in subjects with mild asthma by comparing changes in the two variables after two bronchodilator drugs with pharmacologically distinct mechanisms of action.

In the subjects with mild asthma we studied significant dose related bronchodilatation occurred after both salbutamol and ipratropium bromide in doses up to 1000 μg , and within this dose range ipratropium bromide and salbutamol were equipotent. Previous reports have in general suggested that antimuscarinic agents are less effective bronchodilators than β_2 adrenoceptor agonists in patients with asthma,²⁴⁻²⁶ but these studies have compared conventional clinical doses of the two drugs. Higher doses of ipratropium bromide have been shown to cause greater bronchodilatation than conventional doses in patients with both asthma and chronic bronchitis,²⁷⁻³⁰ but the dose-response relationship of β_2 agonists and ipratropium bromide appear not to have been compared previously in asthmatic subjects.

In our study bronchodilatation with salbutamol was associated with a dose-related decrease in airway reactivity, as described previously with fenoterol.¹⁸ The maximum increase in geometric mean PD_{20} after 1000 μg salbutamol was 2.87 doubling doses of histamine, an increase of the same order of magnitude as that reported after single doses of β_2 agonists.¹¹⁻¹⁶

We did not, however, find a similar dose related change in airway reactivity after ipratropium bromide, even though a similar degree of bronchodilatation was achieved. We saw no evidence of bronchoconstriction after ipratropium bromide, as has been seen in some studies and attributed to the preservative, benzalkonium chloride,³¹ though, because our measurements were carried out 40 minutes after administration of ipratropium bromide, a relatively short lived episode of bronchoconstriction may have gone undetected. It would not easily explain, however, the lack of association between change in PD_{20} and FEV_1 at a time when bronchodilatation had occurred.

Previous studies looking at change in non-specific airway reactivity after single doses of antimuscarinic agents have shown variable results but suggest that the effect is relatively small,²³ ranging from a mean increase in reactivity to histamine by 0.2 doubling doses in one study³² to a maximum reduction in reactivity of 1.5 doubling doses.^{11-14,16} None of these studies has looked at the effect of increasing doses of drugs on bronchial reactivity. The maximum increase in PD_{20} after ipratropium bromide of 0.32 doubling doses in the present study was within the range of increase previously described,²³ though we were unable to demonstrate a dose-response relationship for change in PD_{20} .

When doses of salbutamol and ipratropium that were equipotent in terms of bronchodilatation were compared salbutamol produced a much greater increase in PD_{20} , suggesting that bronchodilatation per se had little effect on airway reactivity. The fact that bronchodilatation with ipratropium was associated with little if any change in airway reactivity is in keeping with the findings of studies that have looked at the effect of cholinergic agonists rather than antagonists on bronchoconstrictor responses. Pre-

constriction with methacholine did not alter histamine PD₃₅, sGaw in the study of Chung and Snashall,³³ nor did it alter the airway response to adenosine in the study of Hardy and colleagues.³⁴ Thus, in general, changes in the level of cholinergic stimulation appear to have relatively little effect on airway reactivity to other pharmacological agonists. How far this is true of other constrictor agonists is more debatable. Some studies have shown an interaction between prostaglandin D₂ and histamine³⁵ whereas others have not,³⁴ and the same is true for other mediators.^{36,37} Such interactions as have been seen have been fairly modest, and it is not clear whether they are pharmacological or physiological in origin.³⁴

Beta agonists have been shown to be functional antagonists on bronchial smooth muscle in vitro,³⁸ causing inhibition irrespective of the contractile stimulus; and this is the likely cause of the reduction in airway reactivity with these drugs in this and other studies. Ipratropium bromide and β agonists have different effects on other aspects of airway function that could affect airway reactivity and airway calibre, such as mast cell mediator release,^{39,40} mucosal oedema formation,⁴¹ and mucociliary clearance;⁴² and β agonists may modulate neurotransmission in parasympathetic ganglia.³⁸ None of these actions, however, as far as they are understood, would easily explain the different effects of β agonists and ipratropium on airway dilatation and reactivity.

Our findings raise the important clinical question of whether the effect of salbutamol on airway reactivity offers clinical benefit over and above bronchodilatation alone. Certain drugs, such as calcium antagonists, have been shown to decrease airway reactivity by up to two doubling doses⁴³ while causing little if any bronchodilatation. These drugs have been disappointing in practice, however,⁴⁴ suggesting that improvement in bronchial reactivity alone may not be of clinical benefit. Clinical trials are therefore indicated to determine whether at equipotent bronchodilator doses β agonists are more effective than antimuscarinic agents in the treatment of asthma and, if they are, to identify the mechanism underlying this advantage.

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