Effects of inhalation of $\beta$-sympathomimetic and atropine-like drugs on airway calibre in normal subjects

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Summary

1. Bronchodilatation was produced in eight normal subjects by inhalation, on separate occasions, of the atropine-like drug ipratropium bromide (0.16 mg by pressurized inhaler; 1 mg nebulized) and the $\beta_2$-sympathomimetic salbutamol (0.8 mg by pressurized inhaler; 5 mg nebulized).

2. Mean specific airways conductance ($sGaw$) increased from a mean value of 0.185 ± 0.002 to 0.292 ± 0.023 s$^{-1}$ kPa$^{-1}$ after ipratropium bromide, and from 0.184 ± 0.020 to 0.303 ± 0.026 s$^{-1}$ kPa$^{-1}$ after salbutamol. These increases in $sGaw$ were not significantly different from each other.

3. During both maximal and partial expiratory flow volume manoeuvres similar increases in flow rates were produced by each drug, at all lung volumes, from 40 to 20% of vital capacity.

4. Changes in maximal and partial flow volume curves after washout of lung air with helium/oxygen (4:1) were measured before and after each drug. Flow rates increased in all subjects and the percentage increase in maximum flow when helium was breathed was not significantly different, when repeated after each drug.

5. Thus our results suggest that salbutamol and ipratropium have similar sites of action, both affecting both large and small airways, and produce similar degrees of bronchodilatation. This is supported by our results after the helium/oxygen breathing, where the lack of change in density dependence of maximal flow suggests that there was no change in the distribution of airways resistance after the drugs.

Key words: $\beta$-adrenoceptor agonists, airway resistance, bronchodilator agents, ipratropium, salbutamol.

Abbreviations: VC, vital capacity; RV, residual volume; $sGaw$, specific airways conductance; MEFV, maximum expiratory flow volume; PEFV, partial expiratory flow volume; $V_{max}$, maximal flow.

Introduction

Both $\beta_2$-sympathomimetic and atropine-like drugs are used in inhaled form in the treatment of the airways obstruction of both asthma and chronic bronchitis [1-4]. These drugs are also known to dilate airways in normal subjects [5, 6].

There has been considerable debate as to the site of action of bronchodilators in the normal bronchial tree [6-9], and the site of airway obstruction in chronic bronchitis and emphysema [10].

Changes in the density dependence of maximum flow during forced expiration, as seen in flow-volume curves with air and less dense gas mixtures breathed, are determined by changes in the relative contributions of small and large airways to the total airways resistance. Previous studies of the site of action of bronchodilators [8, 9] have suggested that cholinergic antagonists predominantly dilate large airways, whereas sympathetic agonists predominantly dilate small airways. There is, however, also evidence that both large and small airway dilatation is produced by each type of drug [6, 11].
To test these differing conclusions we have measured the effects on normal subjects of the atropine-like agent ipratropium bromide (Boehringer Ingelheim Ltd), a quaternary atropine derivative with a pharmacological activity similar to atropine, and the $\beta_2$-sympathomimetic salbutamol (Allen and Hanburys Ltd). We recorded the changes produced by these drugs on a conventional test of airway calibre (specific airways conductance) and on a test of small airway calibre (changes in the maximum expiratory flow rate at $<40\%$ of vital capacity). We have calculated the changes in density dependence of maximum flow, before and after these bronchodilators, to determine the changes in the contributions of large and small airways to total airway resistance. We aimed to assess the bronchodilatation produced by salbutamol and ipratropium bromide in normal subjects, to determine the sensitivity of the methods used to detect the bronchodilatation and finally to assess the site of action of the bronchodilators.

**Subjects and methods**

We studied eight healthy, non-smoking subjects (five women, three men; ages 24–40 years), none of whom had previous history of lung diseases. On separate occasions, in a random order and in a single blind fashion, salbutamol or ipratropium bromide was inhaled, firstly from a pressurized metered dose inhaler, triggered manually by the subject (salbutamol 0.8 mg; ipratropium 0.16 mg), immediately followed by the drug in nebulized form, from an Inspiron mini-nebulizer, inhaled during a period of tidal breathing (salbutamol 5 mg; ipratropium 1 mg). Both forms of inhalation were chosen in order to obtain widespread distribution of the drug, and the doses were chosen so as to produce the maximal dose response (salbutamol, Fig. 1a; ipratropium [11]). Each study was carried out at a similar time of day, only one study being performed per day. We measured airways resistance, lung volumes and maximum and partial expiratory flow–volume curves. Flow–volume curves were obtained before and 1 h after inhalation of each drug, as we have shown maximal response to both drugs occurs 1 h after inhalation (salbutamol, Fig. 1b; ipratropium [11]).

Airway resistance, measured with a modified Du Bois panting technique [12, 13], and lung volumes were measured in a pressure-compensated flow body plethysmograph [14], with rebreathing into a heated humidified bag. Results are expressed as the mean of five technically satisfactory measurements on each occasion. Maximum forced expiratory flow–volume curves (MEFV) were obtained with the subjects seated in a pressure-compensated, volume-displacement body plethysmograph, linked on-line to a PDP 11 computer. Flow at the mouth was measured by a Fleisch no. 4 pneumotachygraph, and lung volume by mixing the plethysmograph spirometer signal and a signal which was proportional to the plethysmograph pressure, resulting in an adequate frequency response in both amplitude and phase for the volume signal. Partial expiratory flow–volume curves (PEFV) were performed with the subject breathing at functional residual capacity for 1 min before exhalation as rapidly as possible from 55–60% of VC to residual volume. We used
Bronchodilatation in normal subjects

FIG. 2. Flow rates during maximal forced expiration. (a) Before (△) or 1 h after (▲) inhalation of (a) salbutamol and (b) ipratropium; means ± SE are shown.

PEFV curves in order to eliminate the inhibition of vagal tone, which can follow inhalation to total lung capacity [15, 16]. The lung volume history was kept constant before each forced expiration, as this has also been shown to influence such manoeuvres [17].

For all flow–volume curves three technically satisfactory curves were obtained for each manoeuvre, the forced vital capacity for three acceptable curves being within 150 ml of one another. Maximal flow rates were measured at 10% intervals of vital capacity, the mean maximal flow rates at a given lung volume of three acceptable curves being used in the analysis. The data were analysed by the t-test for paired observations.

Results

For each subject, airway resistance was not significantly different before inhalation of either drug (P > 0.5). Inhalation of salbutamol produced a significant fall in mean airway resistance of our eight subjects from a control value of 0.162 ± SE 0.020 to 0.092 ± 0.007 kPa 1% s (P < 0.01). Similarly, after ipratropium, airway resistance fell significantly from 0.156 ± 0.019 to 0.104 ± 0.005 kPa 1% s (P < 0.01). Static lung volumes did not change from control volumes after each drug, therefore mean specific airway conductance rose significantly from 0.18 to 0.30 kPa−1 s−1 after salbutamol, an increase of 64%, and from 0.19 to 0.29 kPa−1 s−1, an increase of 58%, after ipratropium bromide (P < 0.001). Changes in airways resistance and conductance produced by either drug were not significantly different from each other.

Fig. 2(a) and 2(b) show a comparison of maximal expiratory flow volume (MEFV) curves before and after each bronchodilator after super-imposing each curve at residual volume. There were no significant differences in control mean maximal flow rates from 40 to 20% of VC before either drug (P > 0.5), thus allowing direct comparison of changes in mean maximal flow rates after bronchodilators. Both salbutamol and ipratropium bromide produced significant increases in flow rates at all lung volumes (P < 0.01). Similar increases in mean maximal flow rates during MEFV were produced by each drug (P > 0.1) at lung volumes between 40 and 20% of VC.

During partial forced expiratory flow–volume (PEFV) curves, Fig. 3(a) and 3(b), control mean flow rates were not different before each drug (P > 0.1). Both bronchodilators produced significant increases in flow, at lung volumes between 40 and 20% of vital capacity (P < 0.01), and as with MEFV curves the increases in flow produced by each drug were not significantly different from each other (P > 0.1).

In a comparison of the increases in maximal flow rates at similar lung volumes during both partial and maximal forced expiratory manoeuvres, before and after salbutamol or ipratropium, control mean flow rates were not different, as measured from either PEFV or MEFV curves at lung volumes between 30 and 20% of VC (P > 0.05), but were significantly greater at 40% of VC on the PEFV curves. Flow rates at the same lung volumes after both bronchodilators were higher during partial as compared with maximal expiratory manoeuvres, these differences being statistically significant (P < 0.01).
The percentage density dependence of maximal flow ($V_{\text{max.}}$) at a given lung volume is defined as:

$$\text{Percentage density dependence of maximal flow} = \frac{V_{\text{max.}}(\text{He}) - V_{\text{max.}}(\text{air})}{V_{\text{max.}}(\text{air})} \times 100$$

Fig. 4(a) and 4(b) show the percentage density dependence at 40% of vital capacity for each individual subject on MEFV curves before and after each bronchodilator. Although individual results were variable the mean density dependence was not significantly changed by either drug ($P > 0.5$). Table 1 shows the mean density dependence results before and after each bronchodilator at 10% intervals of VC from 10% to 20% of VC on MEFV curves and from 40% to 20% of VC on PEFV curves. At each lung volume there was no significant change in mean density dependence after either drug. However, close inspection of Table 1 appears to indicate that the percentage increase in flow breathing helium/oxygen, compared with breathing air, seems to decrease after ipratropium compared with the control value, and, to a lesser extent, appears to increase at most lung volumes after salbutamol,
Bronchodilatation in normal subjects

Table 1. Percentage increases in flow breathing helium/oxygen (4:1) compared with breathing air at each lung volume

Results are means for eight subjects, ± se. For maximal (MEFV) and partial (PEFV) expiratory flow rates both before (control) and after salbutamol or ipratropium, \( P > 0.1 \) in every case.

<table>
<thead>
<tr>
<th>MEFV (%) VC</th>
<th>Control</th>
<th>After salbutamol</th>
<th>After ipratropium</th>
</tr>
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<tbody>
<tr>
<td>50</td>
<td>48 ± 7</td>
<td>60 ± 8</td>
<td>47 ± 4</td>
</tr>
<tr>
<td>40</td>
<td>47 ± 6</td>
<td>50 ± 4</td>
<td>44 ± 4</td>
</tr>
<tr>
<td>30</td>
<td>42 ± 7</td>
<td>48 ± 4</td>
<td>42 ± 5</td>
</tr>
<tr>
<td>20</td>
<td>44 ± 9</td>
<td>42 ± 5</td>
<td>39 ± 5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PEFV (%) VC</th>
<th>Control</th>
<th>After salbutamol</th>
<th>After ipratropium</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>55 ± 6</td>
<td>46 ± 8</td>
<td>61 ± 7</td>
</tr>
<tr>
<td>30</td>
<td>47 ± 5</td>
<td>57 ± 7</td>
<td>55 ± 9</td>
</tr>
<tr>
<td>20</td>
<td>42 ± 5</td>
<td>52 ± 7</td>
<td>45 ± 8</td>
</tr>
</tbody>
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although these differences do not reach statistical significance. In view of this a further analysis of the data was performed, using a paired \( t \)-test, on the absolute flow rates of the eight subjects, when breathing the helium/oxygen mixture, both before and after each drug. There were no significant differences in the flow rates, when breathing helium/oxygen at any of the lung volumes described in Table 1, except at 30% of vital capacity, on a partial flow–volume curve, where the flow rates breathing helium/oxygen were significantly lower (0.02 > \( P > 0.01 \)) after ipratropium, compared with those obtained after the inhalation of salbutamol.

Discussion

In this study we have shown that ipratropium bromide and salbutamol produce similar effects upon airway calibre as assessed by specific airways conductance, forced expiratory flow rates and density dependence. As specific airways conductance reflects large airway calibre, both ipratropium and salbutamol had similar effects in large airways in the doses used. Both drugs produced similar increases in forced expiratory flow rates during both maximal and partial forced expiratory manoeuvres. Forced expiratory flow rates depend, firstly, on the resistance of the airways upstream from the point of flow limitation, whether this be an equal pressure point [18], a collapse point [19] or a choke point [20]. Secondly, flow is dependent on the driving pressure, which is the elastic recoil pressure of the lung. We have assumed that the site of flow limitation and the driving pressure during forced expiration remains constant breathing air or helium/oxygen. Although some authors have described changes in elastic recoil pressure after \( \beta \)-receptor agonists and atropine [5, 16, 21], most studies [6, 9, 11] have found no change in elastic recoil after these drugs. Thus we conclude that salbutamol and ipratropium have similar effects on the resistance of the upstream segment of the airways. As the effect was similar at all lung volumes from 40 to 10% of VC we conclude that the drugs had similar effects on smaller airways [22].

It is generally assumed [23] that flow in the small airways is laminar and independent of gas density, whereas flow in the large airways is disturbed, and thus influenced by gas density. Thus the flow rate response to breathing helium/oxygen, which has one-third of the density of air but a similar viscosity, is indicative of the relative contribution of large and small airways to gas flow resistance. The response to helium/oxygen was not changed either by salbutamol or ipratropium and therefore we conclude that these drugs do not alter the distribution of resistance to air flow and produce a similar degree of bronchodilatation throughout the airways upstream from the site of flow limitation. Although (in Table 1) there appears to be a difference in the response to helium/oxygen breathing after salbutamol compared with the response after ipratropium, as we have described in the Results section, these differences were not statistically significant and more detailed analysis, using the absolute changes in flow rate, revealed statistical significance at only one lung volume, 30% of vital capacity, and only on a partial flow–volume curve. We have no explanation for this single inconsistency.

Thus our results imply that ipratropium and salbutamol have similar effects on airway calibre in both large and small airways. These results conflict with Ingram et al. [9], who found on maximal flow–volume curves that density dependence was increased by isoprenaline and was decreased by atropine, suggesting that isoprenaline dilated small airways, whereas atropine predominantly dilated larger airways. Several differences exist between our own and Ingram's study. The percentage increase in \( V_{\text{max}} \) after each drug in Ingram's study was smaller than in our study (Ingram: isoprenaline 14.8%, atropine 10.6%; this study: salbutamol 24.3%, ipratropium bromide 17.2%). The doses of drugs used in this study were shown to produce maximal bronchodilatation in normal subjects (Fig. 1a) [11]. Ingram used 0.6 mg of atropine sulphate, a drug which is only half as effective on bronchi as ipratropium dose for dose [24], and we have used twice their dosage (1.16 mg
compared with 0-6 mg). Whereas Ingram used 2.5 mg of isoprenaline we administered 5-8 mg of salbutamol, a drug which is as effective in producing bronchodilatation [25]. Furthermore our measurements were made at the time of the maximum effects of the drugs used (Fig. 1b) [11]. No such explanation was given by Ingram of the time after inhalation when measurements were made. Failure to produce maximal bronchodilatation by either drug, either on part or all of the airway would have a profound effect on the interpretation of Ingram’s data. A further difference in Ingram’s study was that measurements were made only on maximal forced expiratory manoeuvres and thus each measurement, both in the control state and after either bronchodilator, was made when the normal vagal bronchokonstrictor tone was inhibited by prior deep inhalation [16, 26]. On the other hand we made measurements both with and without prior inhalation. Ingram quotes only a simple control value. In our study we always compared data with the control value on the day of measurement. Furthermore, Ingram did not measure airway conductance and thus cannot comment on central airway function. We therefore conclude that \( \beta_2 \)-sympathomimetics and atropine-like drugs in normal doses have similar effects on airway calibre throughout the bronchial tree.

We also confirm that maximal expiratory flow rates at the same lung volumes are higher during partial as compared with maximal expiratory manoeuvres, but differences in flow rates were significant \( (P < 0.02) \) only at 40% of vital capacity. After inhalation of either bronchodilator, maximal flow rates at lung volumes between 40 and 10% of vital capacity were higher during the partial compared with the maximal expiratory manoeuvres. These differences were statistically significant \( (P < 0.02) \). Partial expiratory flow–volume curves, therefore, were more sensitive in detecting the effect of bronchodilators in normal subjects than maximal manoeuvres.

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