Comparison of inhaled atropine sulphate and atropine methonitrate

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ABSTRACT The bronchodilator potencies of inhaled atropine sulphate and atropine methonitrate have been compared either alone or in combination with fenoterol in a group of adult asthmatic patients. A cumulative dose response study showed that 2 mg of atropine sulphate produced near maximum bronchodilatation. A larger dose of 4 mg was used in comparing the potency of this drug with 2 mg of atropine methonitrate, a dose previously shown to produce optimum bronchodilatation. In a randomised double-blind fashion atropine methonitrate (2 mg), atropine sulphate (4 mg), fenoterol (400 μg), a combination of atropine methonitrate with fenoterol, a combination of atropine sulphate with fenoterol, and two placebos were administered by inhalation on separate days to eight stable adult asthmatics. Measurements of FEV1 were made before administration of the drugs and at 20 minutes, one, two, four, and six hours afterwards. The two atropine drugs produced a similar peak effect but the bronchodilatation after atropine methonitrate was more prolonged. In combination the bronchodilatation achieved with both atropine drugs and fenoterol was greater than with either atropine or fenoterol alone, confirming that atropine and an adrenergic drug can have an additive effect. The response with atropine methonitrate and fenoterol showed a significant increase in the FEV1 for six hours whereas with atropine sulphate and fenoterol the increase of FEV1 was significantly greater than the placebo for only four hours. It was concluded that the atropine drugs produce useful bronchodilatation either alone or in combination with an adrenergic agent. Of the two atropine drugs, the methonitrate appears to be superior to the sulphate as an inhaled bronchodilator in adult asthmatics.

The anticholinergic drugs atropine sulphate and atropine methonitrate are effective bronchodilators. Moreover, in adults with chronic asthma, optimum doses of atropine methonitrate together with salbutamol produce significantly greater and more lasting bronchodilatation than either drug alone.1 Cavanaugh and Cooper8 have reported that provided an adequate dose is used, atropine sulphate by inhalation is a very effective bronchodilator in asthmatic children, but they did not detect any additive effect when isoprenaline was administered concurrently.

The aim of the present study has been to compare the effectiveness of atropine methonitrate with that of atropine sulphate either alone or in combination with the long-acting adrenergic agent, fenoterol. Optimal doses of the atropine drugs were compared. The dose of atropine methonitrate producing maximum bronchodilatation had been determined previously.1 The optimum dose of atropine sulphate was determined as part of this investigation by examining its dose-response characteristics.

Methods

Thirteen men aged 45–71 years (mean 62 yr) agreed to enter the study. All had features of asthma but were stable when studied. Ten had positive skin tests to multiple allergens, nine fulfilled the MRC criteria for chronic bronchitis, and 10 were taking oral or inhaled steroids or both when studied.

ATROPINE SULPHATE DOSE-RESPONSE STUDY

To examine the dose-response of atropine sulphate, eight of the patients were studied as outpatients while their asthma was stable. Bronchodilators were withheld for at least nine hours before any test. Steroids were continued unchanged.

The technique used was similar to that described...
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by Pierce et al for atropine methonitrate. The atropine sulphate was administered as either 1% or 0·5% aqueous solution inhaled from a Bennett twin nebuliser, powered by air, at a flow rate of eight litres per minute for three seconds, during each full inspiration from close to residual volume. Ten such inhalations delivered 2 mg with the 1% solution and 1 mg with the 0·5% solution. Baseline measurements of FEV₁ were made. The patient then inhaled 2 mg of atropine sulphate. After 40 minutes, further measurements of FEV₁ were made and the patient then inhaled a further 1 mg of atropine sulphate. After a further 40 minutes the FEV₁ was measured again and further 1 mg of atropine sulphate inhaled. Final measurements of FEV₁ were made 40 minutes after the third dose. For each time interval the best of three measurements of FEV₁ was taken and corrected to BTPS. With this technique the cumulative dose was 2 mg, 3 mg, and 4 mg. Measurements of FEV₁ were made on a Godart Spirometer and significance of the results analysed using Student’s t test.

**DRUG COMPARISON STUDY**

For the drug comparison studies, eight of the patients were admitted to hospital in a stable state. Bronchodilators were withheld as in the first study. In a randomised, double-blind fashion on six week days (consecutive where possible), the eight patients were given 2 mg atropine methonitrate, 4 mg atropine sulphate, 400 µg fenoterol, the combination of atropine methonitrate and fenoterol, the combination of atropine sulphate and fenoterol, or two placebos. Each study started at about 0900 m and followed an identical procedure. A wet aerosol was given followed by two puffs from a pressurised metered dose inhaler. In randomised order the wet aerosol contained a 1% aqueous solution of atropine methonitrate, a 2% aqueous solution of atropine sulphate, or water as placebo. To avoid contamination each wet aerosol was given from separate identical containers via a Bennett twin nebuliser as described in the dose-response study. Fenoterol was delivered from a metered dose inhaler (200 µg per puff). An identical inhaler containing only the propellant gases was used as the pressurised aerosol placebo.

The significance of the results was determined by analysis of variance. The baseline FEV₁ was added as a covariate to exclude its influence upon subsequent changes after the drugs.

**Results**

**ATROPINE SULPHATE DOSE-RESPONSE STUDY**

The results of the atropine sulphate dose-response study are shown in fig 1. After 2 mg there was a statistically significant rise in FEV₁ of 32% compared to baseline FEV₁. This approximated the maximum peak response, as with cumulative doses of 3 mg and 4 mg there were further rises of only 1% and 3% in FEV₁ compared to baseline. These increases in FEV₁ were not statistically greater than after 2 mg of atropine sulphate.

Six patients complained of dryness of the mouth or throat. One had dizziness and another had blurred vision.

**DRUG COMPARISON STUDY**

Used singly, both atropine drugs and fenoterol produced a significant increase in FEV₁ compared with the placebo (p < 0·05, fig 2). This was found up to one hour for fenoterol, two hours for atropine sulphate, and six hours for atropine methonitrate. Atropine methonitrate produced significantly higher changes in FEV₁ (p < 0·05) than atropine sulphate at four and six hours, and than fenoterol at six hours. The mean of baseline FEV₁ values, the range of these, and the standard error of mean (SEM) values for each drug and time are shown in the table.

Atropine methonitrate with fenoterol produced a similar degree of bronchodilatation as atropine sulphate with fenoterol (fig 3). Compared with the placebo this lasted for six hours for the former combination, whereas a statistically significant increase of the FEV₁ was obtained for only four hours with the atropine sulphate/fenoterol combination.

The combination of atropine sulphate with
fenoterol produced a significantly higher increase in 
FEV\textsubscript{1} than atropine sulphate alone at 20 minutes, 
two hours, four hours, and six hours, and higher 
than fenoterol alone at 20 minutes, one hour, 
two hours, and four hours.

The combination of atropine methonitrate with 
fenoterol produced a significantly higher FEV\textsubscript{1} than 
fenoterol alone at all times, and after atropine 
methonitrate alone at all times except at six hours.

Fenoterol was well tolerated without any side-
effects, as were placebos. Atropine sulphate pro-
duced dryness of the mouth in three patients and 
giddiness in three. Three patients experienced 
dryness of the mouth with atropine methonitrate. 
Symptoms were less common with the combination of 
drugs.

Discussion

Although our study did not determine the lowest 
possible dose of atropine sulphate which will 
produce maximum bronchodilatation, it did show 
that as a wet aerosol by inhalation a dose of 2 mg 
is adequate, and a dose of 4 mg is more than adequate 
for this purpose. Consequently the failure of a dose 
of 4 mg of atropine sulphate to produce bronchodila-
tation as prolonged as that produced by a dose of 
2 mg atropine methonitrate cannot be attributed to 
an inadequate dose. Instead, it confirms that 
atropine sulphate is less potent than atropine 
methonitrate when both are administered by 
inhalation.

The combination of atropine sulphate with 
fenoterol produced significantly greater broncho-
dilatation than either atropine sulphate or fenoterol 
alone. This result differs from that of Cavanaugh 
and Cooper\textsuperscript{9} who did not obtain any additive effect 
with isoprenaline and atropine sulphate in children. 
This may be because of the different type of patient 
or the use of a short-acting adrenergic agent, as an

Table

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean baseline FEV\textsubscript{1} (l)</th>
<th>Range baseline FEV\textsubscript{1} (l)</th>
<th>Standard error of mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine methonitrate</td>
<td>1.05</td>
<td>0.64-1.67</td>
<td>0.125 0.167 0.148 0.185 0.162 0.173</td>
</tr>
<tr>
<td>Atropine sulphate</td>
<td>1.04</td>
<td>0.50-1.69</td>
<td>0.131 0.172 0.165 0.174 0.133 0.127</td>
</tr>
<tr>
<td>Fenoterol</td>
<td>1.07</td>
<td>0.58-1.76</td>
<td>0.146 0.170 0.163 0.147 0.163 0.153</td>
</tr>
<tr>
<td>Atropine methonitrate + fenoterol</td>
<td>1.00</td>
<td>0.65-1.54</td>
<td>0.121 0.154 0.181 0.159 0.113 0.107</td>
</tr>
<tr>
<td>Atropine sulphate + fenoterol</td>
<td>1.05</td>
<td>0.55-1.52</td>
<td>0.115 0.186 0.169 0.185 0.153 0.115</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.11</td>
<td>0.74-1.68</td>
<td>0.103 0.107 0.111 0.218 0.099 0.121</td>
</tr>
</tbody>
</table>
additive effect has been demonstrated with atropine methonitrate and salbutamol, using optimum doses of each in adult asthmatic patients.\textsuperscript{1} Similarly atropine methonitrate with fenoterol produced greater bronchodilatation than both fenoterol and atropine methonitrate alone in the present study.

Our dose-response study ensured that we had an adequate dose of atropine sulphate, and the studies of Shenfield and Paterson\textsuperscript{9} suggest that the dose of fenoterol used in our study was optimum. Hence, the additive effect demonstrated is unlikely to be the result of suboptimal doses of either drug. It may be related to differences in the pharmacological action of each drug or to differences in receptor sites within the airways. Ingram et al\textsuperscript{4} have reported that atropine has a relatively greater effect than adrenergic stimulants upon larger airways of normal subjects. However, despite this differentiation, the combined effects of atropine sulphate and isoprenaline were not found to be additive in normal subjects when the drugs were combined. Pharmacological differences between the drugs may be more relevant. It has been shown that beta-adrenergic drugs are functional antagonists of cholinomimetics, such as methacholine, whereas atropine is a competitive antagonist.\textsuperscript{5} Functional antagonists act through a separate receptor system without changing the receptors of the spasmogen, whereas competitive antagonists inhibit the spasmogen receptors. Because of this difference in action, the effects of atropine and of adrenergic drugs can be additive. This has been demonstrated in the isolated trachea of animals.\textsuperscript{6} This additive effect using atropine is likely to occur only when bronchoconstriction is through the cholinergic pathway. When spasmogens such as histamine produce bronchoconstriction through other receptors, atropine is unlikely to be an effective bronchodilator. The patients in the present investigation may have been particularly responsive to anticholinergic drugs. They were studied when relatively stable and all those in the drug comparison trial were receiving corticosteroids. Patients with these characteristics are more responsive to anticholinergic drugs than other asthmatics.\textsuperscript{8} We have shown that in such patients, both atropine methonitrate and atropine sulphate alone or with fenoterol, produce useful bronchodilatation by inhalation and that the methonitrate is superior to the sulphate.

References