

# A comparative study of atropine methonitrate, salbutamol, and their combination in airways obstruction

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**ABSTRACT** Dose-response relationships of the cholinergic antagonist, atropine methonitrate, and the beta-adrenergic agonist, salbutamol, were examined by cumulative dose techniques. A wet aerosol, 1.5 mg atropine methonitrate produced a maximum response. The response to 200 µg of salbutamol from a pressurised aerosol was close to maximum. Secondly, the bronchodilator response of salbutamol 200 µg was compared with atropine methonitrate 2 mg and placebo in 18 asthmatic patients in a randomised crossover study. In 11 of them the bronchodilator response of the combination of salbutamol and atropine methonitrate was evaluated. Atropine methonitrate produced a similar peak bronchodilator effect to salbutamol, but its effect was more prolonged, the response being significantly greater at four and six hours than with salbutamol. The combination of drugs produced a significantly greater and more lasting bronchodilatation than either of the drugs alone. Despite mild side effects, atropine methonitrate, either alone or in combination with an adrenergic drug, appears to have a place in the treatment of severe reversible airway obstruction not adequately controlled by conventional treatment.

Substances containing atropine have been used for many decades in the treatment of asthma and several aerosol preparations combining isoprenaline with atropine have been used to give a more lasting effect than isoprenaline alone. These have attracted less attention, however, than the newer beta-adrenergic agonists, such as salbutamol, which similarly provide an increased duration of effect. This study attempts to assess the relative potency of atropine methonitrate, a quaternary ammonium salt of atropine that has a bronchodilator effect in bronchial asthma (Chamberlain *et al*, 1962; Kennedy and Thursby-Pelham, 1964) and in chronic bronchitis (Altounyan, 1964). It has been compared with a standard therapeutic dose of salbutamol, and the bronchodilator effect obtained by combining atropine methonitrate and salbutamol has been assessed.

## Methods

All patients gave informed consent before the studies. In both dose response and comparative trials xanthines were withheld for 48 hours and

adrenergic agonists for at least nine hours before the studies, which started at about 0900. Dose responses for salbutamol and atropine methonitrate were studied in 12 male patients with bronchial asthma. Their clinical characteristics are shown in table 1. Eight patients were studied for each drug, four patients were common to both groups. Measurements were made of the FEV<sub>1</sub>, the best of three readings being taken. In testing salbutamol the technique of Shenfield and Patterson (1973) was used. The patient inhaled one puff from a metered dose inhaler estimated to deliver 100 µg per puff. After this, at five-minute intervals, measurements of the FEV<sub>1</sub> were repeated until there was no further increase. A second puff of salbutamol was then inhaled and measurements taken as before. This was followed by two puffs and the procedure was repeated until the FEV<sub>1</sub> remained unchanged and a final two puffs were administered. In this way the cumulative dose administered was one, two, four, and six puffs. The average duration of the test was 90 minutes (range 70-100).

The peak response to atropine methonitrate is not reached until after about 40 minutes but is

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Table 1 Patients in cumulative dose-response studies

Subject	Age	FEV <sub>1</sub> before salbutamol	FEV <sub>1</sub> after salbutamol	Chronic bronchitis	Current smoker	Skin tests > 2 mm	Steroid treatment
1	58	0.9	1.3	+	-	+	+
2	61	1.5	2.0	+	+	++	+
3	64	2.2	3.0	+	-	+	+
4	65	0.8	1.1	+	-	-	+
5	62	0.5	0.8	+	-	+	-
6	69	0.9	1.2	+	-	-	+
7	63	1.6	2.0	+	+	-	+
8	59	1.2	2.1	+	+	+	+
9	62	0.6	1.0	-	-	+	+
10	70	1.1	1.7	+	+	+	+
11	71	0.7	1.2	+	+	-	+
12	68	1.4	1.9	+	+	+	-
<i>Patients in drug comparison trial</i>							
3, 5, 6, 12 (As above)							
13	57	0.8	1.6	+	-	+	+
14	57	0.9	1.4	-	+	+	+
15	67	0.7	0.9	+	+	-	-
16	66	0.7	1.4	+	-	+	+
17	65	0.4	0.6	+	+	+	+
18	62	0.7	0.8	-	-	++	+
19	58	0.8	1.3	+	-	+	+
20	52	3.4	3.7	+	-	+	+
21	59	1.2	2.2	+	+	+	+
22	64	1.1	1.8	+	+	+	+
23	47	1.5	2.0	-	+	++	+
24	52	0.7	1.7	-	-	+	+
25	51	0.7	0.8	+	-	+	+
26	65	1.1	2.1	+	-	-	+

then usually maintained fairly close to this level for two to three hours. For this reason, after baseline measurements of FEV<sub>1</sub> and the inhalation by the patient of an estimated 1 mg atropine methonitrate, 40 minutes were allowed to elapse before three FEV<sub>1</sub> measurements were made. The measurements were repeated after a further ten minutes to check that there was no further rise in the FEV<sub>1</sub>. A dose of 0.5 mg atropine methonitrate was then inhaled and the measurements repeated as before. A further 0.5 mg was then inhaled and the procedure repeated. For each time interval, the best of three FEV<sub>1</sub> measurements was taken. With this technique the cumulative dose was 1 mg, 1.5 mg, and 2 mg. These doses were delivered via a Bennett twin nebuliser as described below, with the exception that to deliver 0.5 mg of atropine methonitrate, five inhalations of 0.5% atropine methonitrate were used.

The comparative drug trial was performed as an inpatient procedure on 18 male patients with bronchial asthma manifest by a definite history of dyspnoea and wheeze varying spontaneously and responding to bronchodilators. Their symptoms were inadequately controlled by conventional treatment with adrenergic, xanthine, and corticosteroid (oral and inhaled) medication. Their clinical characteristics are shown in table 1. None suffered from glaucoma.

Atropine methonitrate was administered as 1% aqueous solution inhaled from a Bennett twin nebuliser powered by air, at a flow rate of eight litres a minute for three seconds during each full inspiration from close to residual volume. Experiments were conducted that established that ten such inhalations resulted in a dose of about 2 mg. A placebo was administered in the same manner as the atropine solution. Salbutamol, 200 µg, and its placebo were administered as two puffs from unlabelled multi-dose inhalers (MDI). The bronchodilator response of atropine methonitrate, salbutamol, and placebo were compared in all 18 patients. On a separate day, a combination of atropine methonitrate, 2 mg, and salbutamol, 200 µg, were administered to 11 of the patients. The patients were unaware of what drug was being administered on each day. The drugs administered to each individual were given in random order.

Measurements were performed, using a Vitalograph spirometer and a constant volume total body plethysmograph, by observers who were unaware which drug had been administered. Three slow and three forced expiratory manoeuvres were performed and vital capacity (VC) and FEV<sub>1</sub> were measured from the best of the three manoeuvres and corrected to BTPS. Spirometry was recorded before drug administration and at

intervals of 15 minutes, and one, two, four and six hours afterwards, and the increase in FEV<sub>1</sub> ( $\Delta$  FEV<sub>1</sub>) at each of these intervals determined. Pulse rate and symptoms were also recorded at these time intervals. Airways resistance and thoracic gas volume were measured in the plethysmograph before drug administration and two hours afterwards, and specific airways conductance (sGaw) and the static lung volumes calculated. Bronchodilator responses were compared using analysis of covariance.

## Results

### DOSE RESPONSE FOR ATROPINE METHONITRATE AND SALBUTAMOL

Figure 1 shows the salbutamol cumulative dose-response curve. Compared to the mean baseline FEV<sub>1</sub>, there was a rise of 35% after the first 100  $\mu$ g and a further 15% after the second 100  $\mu$ g. Both increases were significant. After the third dose there was an insignificant further rise of 1%. Thus for salbutamol two puffs, a dose of 200  $\mu$ g, produced about maximum response.

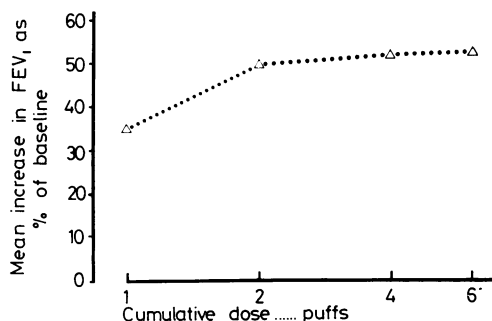


Fig 1 Cumulative dose-response curve for salbutamol in eight patients.

Figure 2 shows the results for atropine methonitrate. One mg of atropine methonitrate produced a mean rise in FEV<sub>1</sub> from the baseline of 36%. There was a further small rise of 10% with the next dose of 0.5 mg. This was not statistically significant. There was no further rise after the third dose of 0.5 mg. Thus maximum bronchodilatation was achieved with a dose of 1.5 mg atropine methonitrate.

### COMPARATIVE DRUG TRIAL

There was little variation in baseline FEV<sub>1</sub> measurements between the study days, and the differences were not statistically significant. The

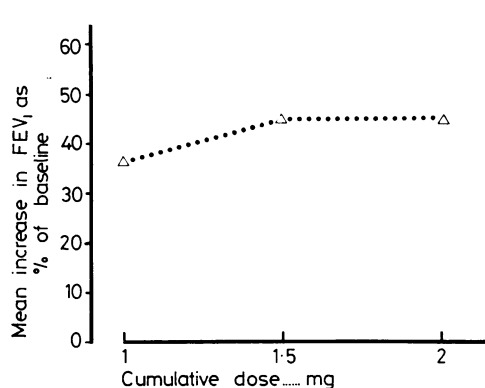


Fig 2 Cumulative dose-response curve for atropine methonitrate in eight patients.

comparisons of the bronchodilator effects of atropine methonitrate, salbutamol, and placebo in the group of 18 patients are shown for FEV<sub>1</sub> and sGaw in table 2. Both atropine methonitrate and salbutamol had substantial bronchodilator effects, which were significantly greater than that of placebo in FEV<sub>1</sub>—up to six hours with atropine and up to two hours with salbutamol. sGaw and the functional residual capacity (FRC) and residual volume (RV) were significantly altered at two hours for both drugs. The peak effects in FEV<sub>1</sub> of the two drugs were similar but that of atropine methonitrate was more prolonged and at four and six hours was significantly greater than with salbutamol. Atropine methonitrate caused a greater fall in lung volumes than salbutamol at two hours, but these differences were not statistically significant.

The results for the combination of atropine methonitrate with salbutamol are shown for FEV<sub>1</sub> and sGaw in table 3. In this group of 11 patients the combination produced a considerably greater and longer lasting effect on FEV<sub>1</sub> than either drug alone, and this difference was significant at two, four, and six hours. This combination produced a significantly greater rise in sGaw than either drug alone, and the fall in total lung capacity (TLC), FRC, and RV were significantly greater than with salbutamol alone.

Only small changes in pulse rate were observed after administration of any of the drugs. There were no flushing or other side effects.

## Discussion

Our results show that atropine methonitrate causes significant bronchodilatation in asthmatic adults. This effect was at least equal to that of

Table 2 Mean increase of FEV<sub>1</sub> (l) (±SD) and mean increase in sGaw after each drug for 18 patients

	Basal FEV <sub>1</sub> (l)	15'	1 h	2 h	4 h	6 h	Basal sGaw (kPa <sup>-1</sup> s <sup>-1</sup> )	Δ sGaw (2 h)
Atropine	1.16 ± 0.71	0.32 ± 0.18***	0.45 ± 0.24***	0.37 ± 0.33***	0.39 ± 0.28***†††	0.23 ± 0.29***††	0.28 ± 0.23	0.28 ± 0.24***
methonitrate	1.12 ± 0.72	0.46 ± 0.30***	0.51 ± 0.30***	0.37 ± 0.22***	0.16 ± 0.13	0.08 ± 0.13	0.25 ± 0.25	0.19 ± 0.17**
Salbutamol	1.14 ± 0.64	0.05 ± 0.12	0.06 ± 0.09	0.06 ± 0.13	0.03 ± 0.18	0.02 ± 0.17	0.25 ± 0.40	0.05 ± 0.07
Placebo								

\*\*\*p < 0.001 } Significantly greater than placebo.  
 \*\*p < 0.01 }  
 ††p < 0.001 } Significantly greater than salbutamol.  
 †p < 0.01 }

Table 3 Mean increase of FEV<sub>1</sub> and sGaw (±SD) after each drug for 11 patients

	Basal FEV <sub>1</sub> (l)	15'	1 h	2 h	4 h	6 h	Basal sGaw (kPa <sup>-1</sup> s <sup>-1</sup> )	Δ sGaw (2 h)
Combination of atropine and salbutamol	0.98 ± 0.54	0.62 ± 0.36***	0.71 ± 0.44***	0.67 ± 0.40***	0.49 ± 0.38***	0.27 ± 0.19***	0.25 ± 0.10	0.50 ± 0.24***
Atropine	0.95 ± 0.57	0.28 ± 0.15**	0.42 ± 0.27**	0.32 ± 0.35**†	0.34 ± 0.26*†	0.14 ± 0.19†	0.24 ± 0.12	0.23 ± 0.22*†
Salbutamol	0.92 ± 0.53	0.41 ± 0.27**	0.46 ± 0.29**	0.31 ± 0.25**†	0.12 ± 0.13†	0.07 ± 0.13†	0.20 ± 0.06	0.18 ± 0.16**††
Placebo	0.89 ± 0.44	0.07 ± 0.13	0.06 ± 0.10	0.07 ± 0.12	0.09 ± 0.15	0.02 ± 0.10	0.22 ± 0.11	0.04 ± 0.05

\*\*\*p < 0.001 } Significantly greater than placebo.  
 \*\*p < 0.01 }  
 \*p < 0.05 }  
 ††p < 0.01 } Significantly less than the combination.  
 †p < 0.05 }

salbutamol and lasted longer. The effectiveness of atropine as a bronchodilator in asthma depends on various factors. When tested, 15 of the 18 patients were receiving corticosteroids and in all the asthma was in relative remission. Atropine had been shown to be more effective in these circumstances than during a severe asthmatic episode or before administration of corticosteroids (Altounyan, 1964). Although patients with chronic bronchitis may respond well to atropine (Crompton, 1968), the presence of chronic bronchitis in 14 of our 18 asthmatics was probably not related to the relative efficacy of atropine. In asthmatics the presence or absence of chronic bronchitis had no influence on the relative efficacy of the cholinergic antagonist, ipratropium bromide, compared with terbutaline (Ruffin *et al*, 1977). The dose of atropine methonitrate used in previous studies was varied considerably. Altounyan (1964) reported that 0.05 mg of atropine methonitrate as a wet aerosol produced maximum bronchodilatation. Kiviloog (1973), on the other hand, used a dose of 2 mg as a wet aerosol. The dose-response curve shows that a maximum peak response was achieved with a dose of 1.5 mg. A dose of 0.05 mg, as advocated by Altounyan, is unlikely to produce a maximal response, whereas the dose of 2 mg used in our drug comparison trial should have ensured this. The observation (Cavanaugh and Cooper, 1976) that a larger dose (0.05 to 0.1 mg/kilo) of atropine sulphate is required to produce maximum response, may be explained by the lesser potency of atropine sulphate compared with atropine methonitrate (Malpass, 1951; Altounyan, 1964; Goodman and Gilman, 1970).

It was of particular interest that although apparently adequate doses were administered, bronchodilatation was appreciably greater when both drugs were administered together. The response to the combination was about equal to the sum of the responses to the drugs individually. We also tested three patients with terbutaline, another adrenergic drug, and the same increased bronchodilator effect as with salbutamol was found when the combination of terbutaline and atropine methonitrate was compared with either drug alone. Chamberlain *et al* (1962) and Kennedy and Thursby-Pelham (1964) previously reported a more prolonged bronchodilator effect from the combination of atropine methonitrate with isoprenaline. Cavanaugh and Cooper (1976) failed to show any potentiation of bronchodilatation when isoprenaline was administered together with atropine sulphate, 0.1 mg/kilo, to asthmatic children. They suggest that the previous results may have

been due to the use of suboptimal doses of atropine. In the present investigation, however, each drug was administered in doses that produced close to maximum bronchodilatation for the drug concerned, so the increased bronchodilatation produced by the combination of the two drugs is unlikely to be due to suboptimal dosage.

The additional bronchodilatation achieved by the combination of the two drugs may be related to differences in their pharmacological action (Offermeier and van den Brink, 1974) or to differences in receptor sites within the airways (Ingram *et al*, 1977). Because of these differences in action, the effects of the two drugs can be additive. This has been shown in the isolated trachea of animals (Offermeier and van den Brink, 1974). When combined with an adrenergic agonist, neither atropine sulphate (Cavanaugh and Cooper, 1976) nor ipratropium bromide have produced significantly greater bronchodilatation than either drug alone (Petrie and Palmer, 1975; Ruffin *et al*, 1977). So far, greater bronchodilatation by the combination of an anticholinergic drug and an adrenergic agonist has been produced in patients only when atropine methonitrate has been used. Evidently this compound is more potent in this regard than other atropine derivatives. We found that for patients with troublesome chronic asthma, the additive bronchodilator response of an optimal dose of atropine methonitrate combined with salbutamol was substantial, as shown by a mean increase of the FEV<sub>1</sub> of 0.7 l.

A disadvantage with atropine methonitrate is that it may produce side effects. Our patients had no significant rise in heart rate or facial flushing after atropine methonitrate. With longer term administration, dryness of the mouth and mild visual blurring for close objects has occurred. In our experience such symptoms have not been severe enough to require cessation of treatment. The patients considered that the benefit of the treatment considerably outweighed the inconvenience of the mild side effects.

Although a pressurised aerosol would be more convenient, when this is not available, atropine methonitrate can be administered as a wet aerosol from a hand nebuliser.

We acknowledge the help of Miss Margaret Rehahn, Cardiothoracic Institute, Brompton Hospital, for statistical advice.

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