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Measurement of pharmacological antagonism produced by atropine in bronchi of normal and asthmatic subjects

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ABSTRACT: The bronchial response of six normal and six asthmatic subjects to increasing concentrations of methacholine aerosol was measured by serial measurements of specific airways conductance (sGaw) in a body plethysmograph. On separate days, the subjects were premedicated with 0.9% NaCl, inhaled atropine at four different doses, or intravenous atropine at two different doses. Cumulative log dose-response curves were constructed. The provocative dose of methacholine needed to cause a 35% fall in sGaw was measured from each curve (PD_{35}). The antagonism produced by a given atropine dose was quantified as the dose ratio, which was defined as the ratio of PD_{35} after atropine to PD_{35} after saline. In normal subjects, approximately equal amounts of atropine given by the inhaled or intravenous routes produced mean dose ratios of almost identical value. However, in asthmatic subjects inhaled atropine (1.28 mg, 4.4 μmol) produced a mean dose ratio 7.5 times greater than the mean value seen with intravenous atropine (1.0 mg, 3.46 μmol). Intravenous atropine (1.0 mg, 3.46 μmol) produced a mean dose ratio of 18.3 for all subjects, compared to a value of 26 predicted from *in vitro* experiments. The slope of the regression line for the relationship of log (dose ratio −1) *vs* −log atropine dose (Schild plot) for all subjects was −0.99. The actions we have observed are compatible with the main actions of atropine being that of a competitive antagonist at the muscarinic receptor. The greater blocking effect of inhaled atropine in some asthmatics suggests that a higher concentration of atropine is achieved at the muscarinic receptor by the inhaled route in these subjects.

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Experiments *in vitro* have demonstrated that atropine is a competitive pharmacological antagonist for acetylcholine at the cholinergic muscarinic receptor [2]. When it is administered by inhalation to man, it blocks the bronchoconstrictive effect of methacholine in a dose dependent fashion and causes bronchodilation [7]. Inhaled atropine has been employed in numerous studies of bronchial responsiveness in man and animals to block airway muscarinic receptors and it is generally assumed that competitive antagonism is its predominant mode of action [8, 10, 19] although other possibilities have been entertained [1]. The main purpose of the present study was to determine whether the quantitative aspects of atropine blockade in man are compatible with competitive antagonism as its main mode of action, or whether the blockade is a function of the atropine-induced bronchodilation. We have examined this question in groups of normal and asthmatic subjects using several doses of inhaled and intravenous atropine.

Methods

Theory

Pharmacological blockade is usually measured by observing the dose of agonist drug required for a particular effect with and without the antagonist being present. The ratio of these doses (dose ratio; DR) is obtained, (but the degree of blockade is indicated by (DR − 1) since when DR = 1 there is no blockade). Blockade is a function of drug concentration and receptor affinity; the relationship is:

$$(DR - 1) = [I]\ K_a$$

where [I] is the competitive antagonist concentration at the receptor, and K_a is the affinity constant of the antagonist-receptor complex. Demonstration of competitive antagonism *in vitro* depends upon showing a simple proportionality between dose and blocking effect over a wide dose range as is predicted by the above equation. This is usually done by plotting log (DR − 1) against −log [I], which is called a Schild plot [2], and with a competitive antagonist this linear relationship has a slope of −1.

Methacholine responsiveness is determined by defining a cumulative dose-response relationship. Response is measured as specific airway conductance (sGaw). We have previously shown that atropine premedication causes a parallel rightward displacement of the methacholine dose-response curve when normalized for changes in airway conductance at the beginning of the challenge [6, 7]. Because the curves are parallel the shift may be quantified by a single number (DR − 1).

Subjects

Six normal and six asthmatic subjects were studied (table I). The normal subjects were laboratory and medical staff. None had present or past history of respiratory illness and none had spirometric evidence of airway obstruction. The asthmatic subjects were attending the Asthma Clinic at Charing Cross Hospital. One of the normal subjects smoked, but none of the asthmatic subjects. All the asthmatic subjects were using a Beclomethasone inhaler regularly, (and had been using it for at least three months). One was using a Salbutamol inhaler regularly, the others were using this medication occasionally. One asthmatic was also using a sodium cromoglycate inhaler regularly. Bronchodilator inhalers were withheld for at least 8 h before each visit and the cromoglycate was withheld for 12 h. No subject had a respiratory infection at the time of study or in the preceding month. Experiments were performed at similar times of the day for each subject, at weekly intervals. No subject allergic to pollen was studied during the pollen season and exposure to other allergens was avoided during the study period. Each subject gave informed consent for the study which was approved by the Charing Cross Hospital Ethical Committee.

Table I. - Subject characteristics

Normal subjects	Sex	Age	FEV_1	FEV_1 % predicted	Skin test (atopy)
1	M	31	4.50	110.2	–
2	Fs	49	2.56	102.4	–
3	F	27	3.37	115.0	–
4	M	35	4.55	103.6	–
5	F	30	3.75	119.0	–
6	M	33	3.52	91.6	+
Asthma subjects					
7	F	49	1.05	39.9	–
8	F	52	1.15	40.1	–
9	M	32	2.30	61.2	+
10	M	45	1.20	35.0	+
11	F	28	2.70	91.5	+
12	M	36	3.30	82.3	+

s = smoker

Methacholine challenge

Airway resistance (Raw) was determined in a constant volume body plethysmograph (Fenyves and Gut, Basle, Switzerland). For each measurement, the subject panted at 1–2 Hz, and the thoracic gas volume (TGV) was determined simultaneously [9]. The output from the plethysmograph was displayed on an X-Y plotter and the slopes were measured manually. To avoid bias, measurements of the records were performed in batches without reference to the dose of atropine administered. Specific airways conductance (sGaw) was expressed as $s^{-1} \cdot kPa^{-1}$ where $sGaw = (Raw \times TGV)^{-1}$. Each determination of sGaw was obtained from the arithmetic mean of five measurements.

Methacholine hydrochloride (molecular weight = 196) dissolved in saline (NaCl solution, 154 mmol/*l*) was delivered intermittently from a Hudson's nebulizer which was attached to a breath activated dosimeter. The nebulizer and dosimeter were triggered by the fall in mouth pressure produced by slow deep inspiration of the subjects from functional residual capacity (FRC). The duration of nebulization was 0.6 s and the volume delivered per actuation was 8 µl. The aerosol produced by the Hudson's nebulizer had a mass median aerodynamic diameter of 2.0 µm (geometric standard deviation = 2.5 µm), as determined by a cascade impactor. The same nebulizer was used to produce the aerosol of atropine sulphate when this was the premedication for the methacholine challenge.

The starting concentration of methacholine in the nebulizer varied from 0.8–25 g/*l* (4.1–128 mmol/*l*) in normal subjects and from 0.01–3.1 g/*l* (0.05–15.8 mmol/*l*) in asthmatic subjects. The same starting concentration of methacholine was used for each of the seven challenges in a given subject. The highest concentration of methacholine used was 200 g/*l* (1.02 mol/*l*) and if adequate bronchoconstriction had not been achieved by five breaths of this solution, then 10, 20 or 40 breaths were inhaled if necessary. These higher doses of methacholine produced transient facial flushing.

Experimental protocol

Each subject had a total of seven methacholine challenges. One challenge was premedicated by an aerosol of saline, four challenges were premedicated by atropine sulphate aerosol and two challenges were premedicated by intravenous atropine sulphate. The aerosol was generated by nebulization of a solution of 4 g/*l* atropine sulphate in saline (13.8 mmol/*l* of atropine) and the doses delivered from the nebulizer on the four occasions were 0.16 mg (0.55 µmol), 0.32 mg (1.1 µmol), 0.64 mg (2.2 µmol), or 1.28 mg (4.4 µmol). The doses of atropine sulphate for intravenous premedication were 0.5 mg (1.73 µmol) and 1.0 mg (3.46 µmol). Atropine and methacholine solutions were prepared freshly each week. Premedicated challenges were performed in random order.

After baseline measurements of sGaw, the subject was premedicated as described above, and after 25 min the sGaw was again measured. This was followed by inhalation of five breaths of saline. After 2 min the sGaw was again measured and the subject then inhaled five breaths of methacholine aerosol. After 2 min the sGaw was again determined. The inhaled concentration of methacholine aerosol was then doubled every 3 min with serial measurements of sGaw 2 min after each series of five breaths. The challenge was terminated when the sGaw had fallen by 50–70% at which point the subject was aware of moderate chest tightness and wheeziness. This was rapidly relieved by the inhalation of 0.2 mg from a salbutamol inhaler. Each methacholine challenge lasted 20–35 min. The methacholine challenge was started 25 min after the atropine because the bronchodilation produced by atropine is maximal 30–60 min after inhalation [11, 12].

To allow comparison of dose-response curves, changes of sGaw were expressed as a percentage of the starting value, after premedication. For each challenge, the specific conductance was plotted against the logarithm to base 10 of the cumulative dose of methacholine delivered to the subject. To define the position of each curve, we determined the cumulative dose of methacholine required to cause a 35% fall in specific airways conductance (PD_{35}). The PD_{35} after no atropine was termed the baseline PD_{35}. We have previously defined the variability of PD_{35} in similar groups of subjects to those used in the present study [7]. Intrasubject coefficient of variation was 13.8% in normal subjects and 25.8% in asthmatic subjects.

The blocking effect of atropine on the methacholine dose-response curve was measured as (DR − 1) where $DR = PD_{35}$ after atropine/baseline PD_{35}.

The change in sGaw produced by atropine premedication was measured by difference between baseline sGaw and post-medication sGaw expressed as a percentage of baseline sGaw.

Statistical analysis

The bronchodilation produced by the different doses of atropine was compared by single factor repeated measurement analysis of variance, with four levels for inhaled atropine and two levels for intravenous atropine. The bronchodilation effect of the different doses of atropine on normal and asthmatic subjects was compared by 2 factor analysis of variance. Similar methods were used to compare values of log (DR − 1) obtained from the challenges.

Results

Baseline sGaw

The mean baseline sGaw for all challenges in normal subjects was 1.63 $s^{-1} \cdot kPa^{-1}$ and in asthmatic subjects was 0.78 $s^{-1} \cdot kPa^{-1}$. The mean coefficient of variation of baseline sGaw (between day) for all challenges in normal subjects was 23.5% and in asthmatic subjects was 18.2%.

Effect of atropine on sGaw

The percentage changes in sGaw at 25 min after atropine premedication are shown in table II. There

Table II. - Percentage increases in sGaw produced by premedication

	Inhaled atropine				Intravenous atropine	
Normal subjects	0.16 mg	0.32 mg	0.64 mg	1.28 mg	0.5 mg	1.0 mg
1	22.1	23.2	21.6	54.9	38.3	23.4
2	56.3	63.5	72.0	69.6	83.8	106.6
3	12.6	–22.3	22.4	24.0	19.2	114.5
4	60.4	60.6	128.8	22.1	40.7	47.7
5	8.0	163.7	52.7	73.7	25.9	85.7
6	32.9	–8.5	41.9	9.1	106.5	47.1
mean	32.1	46.7	56.5	42.2	52.4	70.8
Asthma subjects						
7	42.3	49.4	46.4	100.0	124.5	78.3
8	12.5	72.0	32.1	60.9	76.6	62.5
9	68.1	15.7	55.8	43.1	39.2	50.0
10	70.8	135.1	91.7	176.9	74.4	58.7
11	25.5	42.4	55.9	41.4	57.4	60.9
12	132.4	155.7	88.6	183.3	165.5	350.0
mean	58.6	78.3	61.8	100.9	89.6	110.1

was bronchodilation at every dose of atropine on virtually every occasion. There is no significant difference in the degree of bronchodilation following different doses of atropine, whether given intravenously or by inhalation.

At all doses, there was a greater degree of bronchodilation in asthmatics, but this difference was not statistically significant. There was no significant difference in the degree of bronchodilation produced by inhaled atropine and intravenous atropine in normal or asthmatic subjects. However, there was a significant negative correlation between the percentage increase in sGaw after inhaled atropine and baseline sGaw, when all subjects were analysed together ($r = -0.48$ $p < 0.01$).

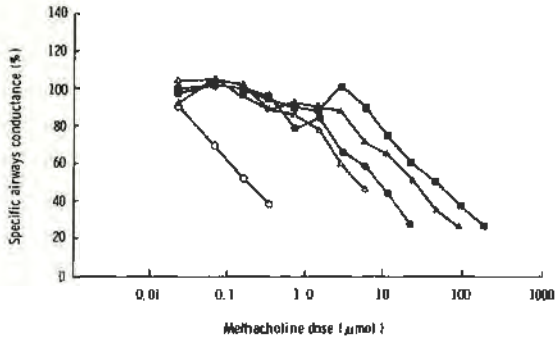

Fig. 1. Cumulative methacholine dose response curves in asthma subject No. 10 after inhaled premedication with the following: saline (○), 0.16 mg atropine (●), 0.32 mg atropine (△), 0.64 mg atropine (▲), 1.28 mg atropine (■).

Baseline PD_{35}

These values are shown in table III. Mean PD_{35} in normal subjects was 19 times greater than in asthmatic subjects, but there was some overlap between the most reactive normal subjects and the least reactive asthmatics.

Effect of atropine on PD_{35}

In each subject, the normalized dose-response curves were approximately parallel (fig. 1) and all doses of atropine in all subjects produced rightward shifts of these normalized curves. The degree of rightward shift, measured as (DR − 1) was a positive function of log atropine dose. (For normal subjects $r = -0.58$, $p < 0.01$; for asthmatic subjects $r = -0.56$, $p < 0.01$) (see fig. 2). However, analysis of variance failed to demonstrate a significant difference in the degree of antagonism produced by the two lowest doses of inhaled atropine in both groups.

There was no correlation between log (DR − 1) and either the percentage increase in sGaw seen at 25 min after atropine administration ($r = 0.073$; $n = 72$) or the absolute value of sGaw at that time ($r = -0.098$).

In some asthmatic subjects considerably larger mean dose ratios were seen at all inhaled atropine doses than in normal subjects (table III), but there was overlap of dose ratios between groups and hence

Table III. - Baseline PD_{35} values and values for (DR–1)

	Baseline PD_{35} (μmoles)	Values for (DR–1)					
		Inhaled atropine				Intravenous atropine	
		0.16 mg	0.32 mg	0.64 mg	1.28 mg	0.5 mg	1.0 mg
Normal subjects							
1	20.6	1.5	1.1	4.8	9.3	3.5	7.9
2	1.2	9.9	13.1	23.4	38.0	18.8	45.4
3	35.0	2.8	7.8	17.4	7.8	3.2	5.5
4	27.2	3.3	1.8	1.7	6.3	5.8	7.2
5	18.6	3.1	5.4	10.8	16.6	3.9	10.2
6	3.3	4.3	8.4	10.9	25.0	10.0	15.7
mean	17.7	4.2	6.3	11.5	17.3	7.5	15.3
Asthma subjects							
7	0.8	0.7	4.6	9.4	35.4	5.9	16.3
8	2.4	1.5	1.0	5.8	12.1	0.8	2.1
9	0.3	22.7	57.2	104.1	295.4	19.6	26.3
10	0.1	43.1	28.7	141.1	242.1	19.1	32.6
11	0.3	26.1	12.5	79.1	290.6	3.5	30.1
12	1.6	1.1	2.7	6.3	17.2	3.8	8.9
mean	0.9	15.9	17.8	57.6	148.8	8.8	19.4

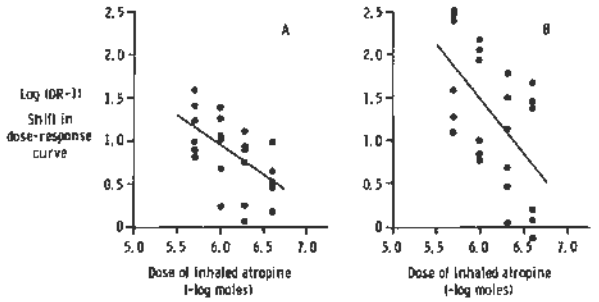

Fig. 2. Schild plots for inhaled atropine. A, normal subjects; B, asthmatic subjects.

the differences were not statistically significant ($p = 0.2$). The differences in the means were largely due to three asthmatic subjects (Nos 9–11) with dose ratio approximately ten times greater than the remaining subjects. In contrast, mean dose ratios to intravenous atropine showed little difference between normal and asthmatic subjects, and the three asthmatic subjects with very large dose ratios to inhaled atropine had unremarkable dose ratios to intravenous atropine.

To quantify the inhaled-intravenous difference in shift of the dose-response curves, we have compared (DR − 1) obtained following 0.5 and 1.0 mg intravenous atropine with the interpolated values for inhaled atropine at these doses. For each subject, we interpolated between inhaled doses using a linear regression of log (DR − 1) against log dose. In asthmatic subjects at both these doses significantly higher dose ratios were obtained with inhaled atropine when compared to intravenous atropine ($p < 0.01$ at 1.0 mg; $p < 0.02$ at 0.5 mg). By contrast in normal subjects there were no significant differences in dose ratios obtained using the two routes of administration. The difference between inhaled and intravenous dose-ratios was significantly greater in asthmatic subjects than in the normal subjects ($p < 0.01$ at 1.0 mg; $p < 0.05$ at 0.5 mg). A comparison of the highest inhaled and intravenous doses is shown in figure 3.

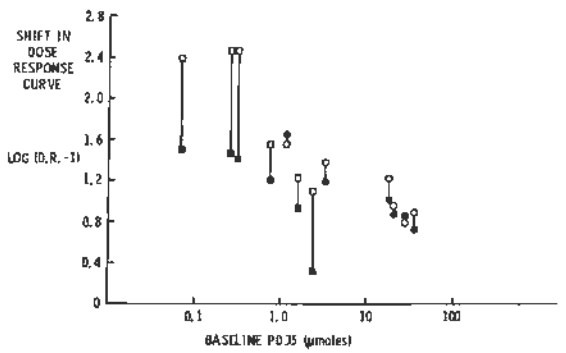

Fig. 3. The relationship between methacholine sensitivity (PD_{35}), shift in the dose-response curve (log dose ratio − 1), and route of administration of atropine. Normal subjects 1.28 mg atropine inhaled (○), normal subjects 1.0 mg atropine *i.v.* (●), asthma subjects 1.28 mg atropine inhaled (□) and asthma subjects 1.0 mg atropine *i.v.* (■).

Table IV. - Correlation coefficients of relationship between log (DR–1) and log PD_{35}

	Normal	Asthma	All subjects
Atropine dose			
Inhaled			
0.16 mg	0.82*	0.86*	0.61*
0.32 mg	0.53	0.85*	0.63*
0.64 mg	0.62	0.93*	0.66*
1.28 mg	0.93**	0.83*	0.89***
Intravenous			
0.5 mg	0.94**	0.82*	0.45
1.0 mg	0.96**	0.86*	0.65*

* = $p<0.05$, ** = $p<0.01$, *** = $p<0.001$. All coefficients above are negative.

Relationship between (DR − 1) and baseline PD_{35}

Subjects who were most sensitive to methacholine were those who had the highest blockade from atropine. The correlation coefficients of the relationship between log (DR − 1) and log baseline PD_{35} are shown in table IV. The relationship between log baseline PD_{35} and log (DR − 1) values for the highest doses of inhaled and intravenous atropine are shown in figure 3.

Schild plots

The relationship between log (DR − 1) and −log dose atropine is shown for all subjects in figure 2. The mean slope of the regression line was −0.69 in normal subjects and −1.29 in asthmatic subjects. For all subjects the mean slope was −0.99.

Discussion

We have observed a dose-dependent antagonism of methacholine induced bronchoconstriction with both inhaled and intravenous atropine. This is unlikely to be caused by bronchodilation since the degree of bronchodilation, however quantified, showed no dose-dependency.

The mean Schild plot slope was close to that expected for a competitive antagonist, but intersubject differences and a limited dose range weaken this evidence. Individual subjects' Schild plot slopes differ markedly but this might be expected when one considers that the intrasubject variability of PD_{35} measurements is approximately 2-fold and the total range of atropine doses used was only 8-fold. Significant Schild plot correlation coefficients (r more negative than −0.95) were obtained in only six of the twelve subjects. Thus, although our Schild plot analysis is compatible with competitive antagonism as

the predominant mode of action of atropine, it can hardly be said to be conclusive evidence.

The degree of antagonism we observed with intravenous atropine is close to that which would have been predicted knowing the potency of atropine as a competitive antagonist *in vitro*. We have been unable to find *in vitro* measurements of the antagonism of atropine at the human bronchial muscarinic receptor, but antagonism is similar in various tissues and species for a given antagonist-atropine combination [5]. The plasma atropine concentration 30 min after an intravenous injection of 1 mg atropine is approximately 5 ng/ml ($10^{-7.7}$ molar) [4]. This concentration *in vitro* produces a value for (DR − 1) of 25 [2]. The mean value for all our subjects for (DR − 1) was 17.3.

In this study we have used a single control measurement of PD_{35} (baseline PD_{35}) and have related all the premedicated challenges to this. Spontaneous changes in responsiveness during the course of this study should have a random effect on the Schild plot slope and position. The baseline PD_{35} determines the vertical position of the Schild plot, but not its slope. In any one individual, studies were performed over a period of two months and it was therefore necessary to choose stable subjects, and in fact all of them were well controlled on inhaled corticosteroids. Non-specific bronchial responsiveness remains similar over long periods when exacerbating factors are not present [17]. Two asthmatic subjects had values for PD_{35} higher than we have previously observed, possibly due to long-term treatment with inhaled corticosteroids.

If it is accepted that: 1) atropine is predominantly acting as a competitive antagonist and 2) we can quantify this antagonism with *in vivo* bronchial dose-response curves, then it follows that the wide intersubject differences in dose-ratios to inhaled atropine are due to differences in atropine concentration or in receptor affinity for atropine.

ITKIN and ANAND [16] first described the difference in efficacy between inhaled and intravenous atropine in asthmatic subjects. SHEPPARD *et al.* [21] compared the blocking effect of 0.5 mg of atropine given either intravenously or by inhalation to asthmatic subjects, using techniques similar to our own. From their data we calculate a mean (DR − 1) of 10.1 for intravenous atropine and greater than 270 for inhaled atropine. Inhaled atropine was more than 27 times more effective in blocking methacholine than intravenous atropine in their study and approximately 10 times more effective in our study. Their subjects were on average more responsive to methacholine than our subjects. In our study the subjects with the greatest inhaled/intravenous difference were the most responsive to methacholine.

SHEPPARD *et al.* did not study normal subjects. We have shown that atropine was of equal potency by the two routes of administration in normal subjects. We suggest that in normal subjects approximately equal atropine concentrations are achieved at the muscarinic receptor by the two routes of administration whereas in asthma much higher atropine concentrations are achieved by inhalation at least at certain points in the bronchial tree.

Asthma is associated with bronchial epithelial damage [18] and this could increase epithelial permeability. However, this is unlikely to affect the penetration of atropine sulphate which is lipid soluble and therefore crosses normal epithelium with ease.

Our subsequent studies have quantified aerosol deposition in the bronchi using the same apparatus and inhalation technique as in the present experiments. In normal and asthmatic subjects similar proportions of inhaled drug reach the tracheobronchial tree but in asthma deposition tends to be patchy and more central [13]. The degree of uneveness of deposition correlated positively with atropine (DR − 1). Our hypothesis is that in normal subjects atropine deposits evenly over a large bronchial surface area, achieving low concentrations and low (DR − 1). Methacholine is similarly distributed and this may be a factor in determining the low sensitivity of the normal subject to this agent. By contrast, in asthma both atropine and methacholine tend to deposit focally in central bronchi. In a given individual it is reasonable to expect the distribution patterns of these two agents to be similar. The parts of the bronchial tree that receive the highest methacholine concentration will contribute most of the overall bronchoconstrictor response, and these parts will also receive a high concentration of atropine, giving a high value for (DR − 1). Intravenous administration of atropine results in an even distribution to the bronchi in both groups and hence the antagonistic effect produced is relatively modest and similar in normal and asthmatic subjects.

If the above explanation is correct, then the same principles may apply to functional pharmacological interactions, such as that between beta-adrenergic agonists and methacholine. Thus, inhaled isoprenaline used to antagonise inhaled methacholine produced higher dose ratios in asthmatic subjects [14] and we have previously reported an enhanced antagonistic effect of salbutamol on methacholine bronchoconstriction in asthmatic subjects [23].

At each concentration of intravenous atropine we observed a 20-fold intersubject range in dose ratios. From the study of HARRISON *et al.* [15] we predict an intersubject range of plasma atropine concentration of only approximately 3-fold at 30 min from the injection. The greater range of dose ratios could result either from differences in bronchial muscle perfusion or receptor affinity.

At most atropine doses and with both routes of administration the dose-ratio correlated negatively and significantly with PD_{35} (fig. 3, table IV). This is to be expected if the same factors of concentration and receptor affinity are responsible for the responsiveness to atropine and methacholine. We have demonstrated a similar phenomenon for the interaction between histamine and chlorpheniramine [16]. However, in

plotting (DR − 1) against PD_{35}, it should be noted that PD_{35} features on both axes (DR = PD_{35} after atropine/baseline PD_{35}). If baseline PD_{35} is underestimated, (DR − 1) will be overestimated and a relationship of the type shown in figure 3 may be seen. However, it is difficult to dismiss entirely the relationship between log (DR − 1) and log PD_{35} in this way, since it occurs over a wide range of values for baseline PD_{35} (350-fold range) and of (DR − 1) (22–83-fold range) in the correlations at different doses with correlation coefficients as good as −0.96.

We have therefore found two relationships in these subjects' responses to atropine, both to some extent dependent on the individual's baseline PD_{35}. The first relationship is that the subjects most sensitive to methacholine have larger inhaled/intravenous differences in atropine dose-ratios. The second relationship is that the subjects least sensitive to methacholine (with large PD_{35} values) tend to have low values for atropine antagonism, whether administered by the intravenous or inhaled route. Conversely subjects with low PD_{35} values have higher values for atropine antagonism.

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References

1. Altounyan REC. – Variation of drug action on airway obstruction in man. *Thorax*, 1964, 19, 406–415.
2. Arunlakshana O, Schild HO. – Some quantitative uses of drug antagonism. *Brit J Pharmacol*, 1959, 14, 48–58.
3. Barnes PJ, Basbaum CB, Nadel JA. – Autoradiographic localisation of autonomic receptors in airways smooth muscle. *Am Rev Resp Dis*, 1983, 127, 758–762.
4. Berghem L, Bergman U, Schildt B, Sorbo B. – Plasma atropine concentrations determined by radioimmunoassay after single IV and IM administration. *Brit J Anaesth*, 1980, 52, 597–601.
5. Bowman WC, Rand MJ. – Textbook of pharmacology, 2nd Edition. Principles of drug action; Blackwell Scientific Publications. London, 1980, pp 39.1–39.69.
6. Chung KF, Morgan B, Keyes SJ, Snashall PD. – Histamine dose-response relationships in normal and asthmatic subjects. *Am Rev Resp Dis*, 1982, 126, 849–854.
7. Chung KF, Snashall PD. – Methacholine dose-response curves in normal and asthmatic man. Effect of starting conductance and pharmacological antagonism. *Clin Sci*, 1984, 66, 665–673.
8. Deal EC Jr, McFadden ER Jr, Ingram RH Jr, Jaeger JJ. – Effect of atropine on potentiation of exercise-induced bronchospasm by cold air. *J Appl Physiol*, 1978, 45, (2), 238–243.
9. Dubois AB, Botelho SY, Comroe JH. – A new method for measuring airways resistance in man using a body plethysmograph: Values in normal subjects and patients with respiratory disease. *J Clin Invest*, 1956, 35, 327–35.
10. Fish JE, Rosenthal RR, Summer WR, Menkes H, Norman PS, Permutt S. – The effect of atropine on acute antigen-medicated airway constriction in subjects with allergic asthma. *Am Rev Respir Dis*, 1977, 115, 371–379.
11. Gal TJ, Suratt PM. – Atropine and glycopyrrolate effects on lung mechanics in normal man. *Anesth Analg*, 1981, 60, 85–90.
12. Gal TJ, Suratt PM, Lu JY. – Glycopyrrolate and atropine inhalation: Comparative effects on normal airway function. *Am Rev Resp Dis*, 1984, 129, 871–873.
13. Gillett MK, Briggs BA, Snashall PD. – Central deposition of aerosols as a determining factor in bronchial responsiveness. *Clin Sci*, 1986, 71, Suppl 15, 82p.
14. Greenspon LW, Morrissey WL. – Factors that contribute to inhibition of methacholine-induced bronchoconstriction. *Am Rev Resp Dis*, 1986, 133, 735–739.
15. Harrison LT, Smallridge RC, Lasseter KC, Goldlust MB, Shamblen EC, Gam VW, Chang SF, Kvam DC. – Comparative absorption of inhaled and intramuscularly administered atropine. *Am Rev Resp Dis*, 1986, 134, 254–257.
16. Itkin IH, Anand SC. – The role of atropine as a mediator blocker of induced bronchial obstruction. *J Allergy*, 1970, 45, 178–186.
17. Juniper EF, Frith PA, Hargreave FE. – Long term stability of bronchial responsiveness to histamine. *Thorax*, 1982, 37, 288–291.
18. Laitinen LA, Heino M, Laitinen A, Kava T, Haahtela T. – Damage of the airway epithelium and bronchial reactivity in patients with asthma. *Am Rev Resp Dis*, 1985, 131, 599–606.
19. Nadel JA, Salem H, Tamplin B, Yokiwa Y. – Mechanisms of bronchoconstriction during inhalation of sulphur dioxide. *J Appl Physiol*, 1965, 20, 164–167.
20. Pedley CJ, Schroter RC, Sudlow MF. – The prediction of pressure drop and variations of resistance within the human bronchial airways. *Respir Physiol*, 1970, 9, 387–405.
21. Sheppard D, Epstein J, Holtzman MJ, Nadel JA, Boushey HA. – Effect of route of atropine delivery on bronchospasm from cold air and methacholine. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1983, 54, (1), 130–133.
22. Snashall PD. – *In vivo* and *in vitro* responsiveness off bronchial smooth muscle. *Bull Eur Physiopathol Respir*, 1986, 225, Suppl 7, 212–227.
23. Snashall PD. – Mechanisms of hyperresponsiveness: General Review. *In*: Bronchial responsiveness. JA Nadel, R Pauwels, PD Snashall, eds., Blackwell Scientific Publications, London pp. 257–314.

RÉSUMÉ: La réponse bronchique à l'inhalation d'un aerosol de methacholine à concentrations croissantes a été évaluée chez six sujets normaux et six asthmatiques par la mesure de la conductance spécifique des voies aériennes (sGaw) dans un pléthysmographe corporel. Les sujets étaient prétraités par 0.9% NaCl, de l'atropine inhalée à 4 doses différentes ou de l'atropine *i.v.* à 2 doses différentes. Des courbes cumulatives log dose-réponse ont été construites et la dose de methacholine nécessaire pour provoquer une chute de sGaw de 35% a été mesurée sur chaque courbe (PD_{35}). L'antagonisme produit par une dose donnée d'atropine a été quantifiée par le rapport entre PD_{35} après atropine et PD_{35} après 0.9% NaCl appelé rapport de doses. Chez les sujets normaux les rapports de doses moyens sont presque identiques lorsque des doses approximativement égales d'atropine sont administrées par voie *i.v.* on par inhalation. Par contre chez l'asthmatique l'inhalation de 1.28 mg (4.4 µmol) d'atropine induit un rapport de doses moyen 7.5 fois plus élevé que la valeur moyenne observée après injection *i.v.* de 1.0 mg (3.46 µmol) d'atropine. L'atropine *i.v.* (1.0 mg, 3.46 µmol) produit pour tous les sujets un rapport de doses de 18.3, à comparer à une valeur de 26 prédite à partir d'experimentations *in vitro*. La pente de la droite de régression décrivant la relation log (rapport de dose − 1) versus − log dose d'atropine pour tous les sujets valait −0.99. Nos observations sont compatibles avec l'hypothèse selon laquelle l'atropine agit principalement comme un antagoniste compétitif au niveau des récepteurs muscariniques. L'effect bloquant supérieur obtenu chez certains asthmatiques avec l'atropine inhalée suggère que chez eux une concentration d'atropine plus élevée est obtenue par l'inhalation au niveau des récepteurs muscariniques.