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Site of action of ipratropium bromide and clinical and physiological determinants of response in patients with asthma

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ABSTRACT It has been suggested that in normal subjects inhaled anticholinergic agents have a preferential dilating effect on large central airways. We therefore studied 21 patients with asthma to see if response to inhaled ipratropium bromide was related to the initial central or peripheral site of major airway narrowing. Fourteen out of 21 patients with asthma increased their $\dot{V}max$ more than 10% after ipratropium but when assessed by air and helium/oxygen (He/O_2) flow-volume curves, responders and non-responders to He/O_2 breathing were divided equally between those who benefited from the drug, and those who did not. There were no significant differences in percentage improvement in $\dot{V}max$ between initial responders, and initial non-responders to He/O_2 breathing. Furthermore the results from air and He/O_2 flow-volume curves suggest that, contrary to some previous reports (not in asthmatics), inhaled ipratropium has a generalised action throughout the airways. There were no differences in severity of airflow obstruction, nor in age, sex, smoking history, or atopic status between those who benefited from ipratropium and those who did not. However, those improving after the drug had a significantly longer history of asthma than those who did not.

Although resting vagal tone is normally present throughout the bronchial tree,[1] it has been claimed that in normal subjects inhaled anticholinergic agents act mainly on the large central airways,[1-3] although Douglas and colleagues[4] disagree.

In some patients with asthma the helioxygen technique[5] suggests that the major site of narrowing is in the larger central airways, whereas in others the main obstruction is more peripheral.

If the anticholinergic agent ipratropium acts mainly on large airways, it should be more effective in patients with predominant large airway obstruction, and this is the hypothesis tested here. The use of the helioxygen technique to test the effect of ipratropium in asthmatic patients has not been reported previously.

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Methods

Twenty-one patients with airflow obstruction which had been shown to vary spontaneously or with treatment took part in the study and their clinical details are shown in table 1. Atopic status and smoking status were categorised in the same way as by Antic and Macklem.[6] All patients attended the laboratory in an afternoon having had no bronchodilator for at least 12 hours. Flow-volume curves were obtained using an Ohio 840 electronic spirometer from which flow and volume signals were taken to an Electronics for Medicine DR8 photographic recorder. The patients performed a minimum of three forced expirations breathing air and results were accepted only if the vital capacity was reproducible to within 100 ml. Three further forced expirations were then performed after breathing a mixture of 80% helium, 20% oxygen (He/O_2) until end-tidal nitrogen concentration was less than 5% when measured by a mass spectrometer (Centronics MGA

Table 1 *Details of patients studied*

	Age (yr)	*Sex*	*Smoking history*	*Duration of asthma (yrs)*	*Atopic status**
1	44	M	NS	9	−
2	56	F	S	36	−
3	24	M	S	5	+
4	56	M	NS	20	−
5	71	M	NS	60	−
6	51	F	ES	1	−
7	69	F	NS	2	−
8	69	M	S	1	−
9	24	M	NS	11	−
10	59	F	NS	1	−
11	63	F	NS	4	−
12	37	M	NS	3	+
13	22	F	S	20	+
14	67	F	NS	3	−
15	52	F	NS	5	−
16	21	M	S	11	+
17	50	M	S	8	−
18	69	F	S	3	−
19	69	F	ES	5	−
20	72	M	ES	30	−
21	45	M	S	35	+

*Atopic status (− or +) and smoking history (NS = non-smoker, ES = ex-smoker, S = smoker) classified in the same way as by Antic and Macklem[4].

200). Flow rates at 50% of vital capacity ($\dot{V}max_{50}$) were measured at BTPS and the mean flow rate from at least three curves obtained breathing air compared with those on He/O_2 and expressed as percentage change (the "density dependence") by the formula:

$$\Delta \dot{V}max_{50}\% = \left(\frac{\dot{V}max_{50} \text{ on } He/O_2}{\dot{V}max_{50} \text{ on air}} - 1\right) 100$$

Those with a greater than 20% response to He/O_2 breathing were termed "responders" and those with a less than 20% response termed "non-responders".[5]

The patients then inhaled four puffs of ipratropium bromide (0·08 mg) and air and He/O_2 flow-volume curves were repeated 30 minutes later. Results are expressed as a percentage improvement over baseline and compared by the paired *t* test. Seven patients also had measurements of residual volume (RV) and total lung capacity (TLC) made in a Dubois-type body plethysmograph before and after inhalation of ipratropium. Maximum flow rates could then be compared at the same absolute lung volume before and after the bronchodilator, independently of changes in TLC, RV, or VC. We selected a volume as close as possible to 50% vital capacity before ipratropium such that flow rate could be measured at that same volume after bronchodilatation on the downstroke of the second flow-volume curve.

Results

Mean values of flow rates and vital capacity in the 21 patients were significantly improved after ipratropium but there was no significant difference between the mean response of $\dot{V}max_{50}$ to He/O_2 breathing before ipratropium compared with after inhalation of the drug (table 2). Results from the seven patients studied in the plethysmograph show significant changes in mean values of residual volume and total lung capacity after inhalation of the drug (table 3), but again there were no differences in the flow rate responses to He/O_2 at the same absolute lung volume before and after ipratropium.

Whereas all patients had on other occasions shown a minimum 10% improvement in $\dot{V}max$ after inhaled β_2 agonists, only 14 of the 21 patients given ipratropium showed a similar improvement. Of these 14 patients who benefited from ipratropium, eight had been inital responders to He/O_2 breathing ($\Delta\dot{V}max_{50} > 20\%$) and six had been initial non-responders ($\Delta\dot{V}max_{50} < 20\%$). Of the seven patients who did not improve $\dot{V}max$ by 10% or more after ipratropium, four were responders to He/O_2 breathing and three were non-responders (table 4). When magnitude of improvement of $\dot{V}max$ after ipratropium was related to initial major site of airway narrowing, the mean percentage improvement in $\dot{V}max$ after ipratropium was 24·5% (± 18·9) in those with their initial major site of flow limitation in the larger central airways (responders to He/O_2 breathing), against 15·5% (± 17·8) among those with preferential peripheral airway constriction (non-responders to He/O_2 breathing)—a non-significant difference.

Table 2 *Effect of ipratropium bromide on indices derived from the flow-volume curves obtained while breathing air helium/oxygen mixtures*

	Mean values (with standard deviation) n = 21		*Mean percentage improvement after ipratropium (with SD)*	*Statistical significance of change* p <*
	Before ipratropium	*After ipratropium*		
Vmax breathing air (l/s)	4·25 (± 1·42)	4·96 (± 1·46)	+20·4 (± 18·6)	0·001
$V max_{50}$ breathing air (l/s)	1·07 (± 0·83)	1·33 (± 1·05)	+29·5 (± 31·3)	0·005
$Vmax_{25}$ breathing air (l/s)	0·37 (± 0·31)	0·44 (± 0·40)	+23·8 (± 31·9)	0·002
Vital capacity (l)	3·10 (± 1·10)	3·42 (± 1·07)	+ 12·9 (± 15·5)	0·001
Percentage improvement in $Vmax_{50}$ breathing He/O_2 compared with air	24·7 (± 20· 8)	30·1 (± 23·5)		NS

* Paired *t* test. NS = not significant.
Vmax is equivalent to peak expiratory flow rate.
$Vmax_{50}$ and $Vmax_{20}$ refer to maximum flow rates at 50 and 25% of vital capacity.

Table 3 *Lung volumes and flow rate responses to helium/ oxygen breathing in the seven patients studied in a plethysmograph before and after ipratropium*

	Mean values (with standard deviation)		*Statistical significance of change* p <*
	Before ipratropium	*After ipratropium*	
Residual volume (l)	4·37 (± 2·8)	2·84 (± 1·2)	0·001
Total lung capacity (l)	6·80 (± 2·8)	5·78 (± 2·0)	0·001
Density dependence of flow rates at same absolute lung volume, He/O; compared with air (%)	+34·7 (± 20·9)	+33·3 (± 23·7)	NS

* Paired *t* test. NS = not significant.
All flow rates after ipratropium were measured at the same volume as before ipratropium (see text).

Table 4 *Response to ipratropium related to initial response to He/O_2 breathing. Vmax is the peak expiratory flow rate (PEFR)*

	Response of Vmax (PEFR) to ipratropium	
	< 10% increase	*> 10% increase*
Δ $Vmax_{50}$ (He/O_2) < 20% increase	3	6
Δ $Vmax_{50}$ (He/O_2) > 20% increase	4	8

There were no differences in severity of airflow obstruction, nor in age, sex, smoking history, or atopic status between the 14 patients who benefited from ipratropium and those who did not. However, those improving after the drug had a significantly longer history of asthma (mean 20·4 years ± 19·9) than those who did not improve (mean 6·2 years ± 10·2, unpaired *t* test $p < 0·05$).

Discussion

The technique of comparing air and He/O_2 flow-volume curves is a widely accepted method of determining the main site of airway narrowing, and the theoretical background[5 7] is supported by validation in dogs.[8] However, the actual size of airways where a laminar and therefore density independent flow regime prevails may be surprisingly large.[9] Using this technique, Ingram and colleagues[2] have suggested that in normal subjects inhalation of anticholinergic agents is associated with preferential large airway dilation. Hensley and colleagues[3] have measured anatomical dead space before and after inhaled atropine in normal subjects, and reviewed published reports to suggest that this measurement is weighted towards dimensional changes in the more proximal conducting airways. They have shown increases in anatomical dead space after atropine and interpret the findings (by a comparison with the peripheral effects of isoprenaline) to confirm that the predominant site of action of inhaled atropine is on the larger central airways. De Troyer and colleagues[1] have compared the effects of large doses of inhaled ipratropium bromide with those of intravenous atropine, and suggested that the bronchodilation produced by the inhaled drug is confined to the large airways, whereas intravenous atropine has an additional peripheral airway effect.

In our 21 patients with asthma the mean density dependence ($\Delta \dot{V}max_{50}$% He/O_2) after ipratropium was the same as before inhalation of the drug. This suggests that there was no systematic change in the site in the airways at which maximum flow is determined (the flow-limiting segment). However, when comparing flow rate response to He/O_2 breathing before and after administration of a drug, when there may be significant changes in vital capacity, $\dot{V}max_{50}$ may be difficult to interpret if absolute lung volumes are not measured. Under such circumstances although flow rates at 50% of exhaled vital capacity are being compared each time, because of changes in residual volume and total lung capacity the absolute lung volume at which measurements are being made may well be different. To counteract this source of error we did measure flow rates at the same absolute lung volume in a smaller subgroup of seven patients. Flow rate response to He/O_2 breathing at the same absolute lung volumes was not significantly different after the drug compared with before and we therefore feel that the conclusions drawn from the results of the whole group are valid. Although most previous workers have suggested that the action of ipratropium is localised to the larger central airways in normal subjects, our findings are consistent with more recent studies on normal subjects[4] and on patients with chronic bronchitis[1 0] in whom inhaled ipratropium also had a generalised action.

These different findings are unlikely to be the result of drug dosage, for a central preferential effect has been claimed in normal subjects[1] using three times the dose used by ourselves and Douglas and colleagues.[4 1 0] They are also unlikely to be caused by the techniques of assessment because contradictory results have been achieved with the same

techniques[1 4] and concordant results with different techniques.[2 3] One source of difference might be a patchy distribution of narrowing in asthmatic subjects, with narrowing at segmental levels in some parts of the lung and in smaller airways in others.

Whatever the reason for the lack of correlation between initial site of major narrowing and response to ipratropium, this finding apparently precludes the possibility of prescribing different bronchodilators according to an individual patient's site of major obstruction—for example, ipratropium for a patient with large airway obstruction.

We therefore looked for other clinical or physiological features which might predict response to ipratropium. There were no differences in severity of airflow obstruction, nor in age, sex, smoking history, or atopic status between those who benefited from ipratropium and those who did not. However, those who benefited from the drug had a significantly longer history of asthma than those who did not. This may imply that cholinergic influences become relatively more important in determining bronchial calibre with length of history of disease. Whether this is the result of an increase in vagal tone or possibly a loss of number or function of β receptors remains uncertain.

Others have suggested that patients with chronic bronchitis respond well to ipratropium bromide.[10] Some of our patients with asthma had chronic productive cough—although we did not formally assess these symptoms—but parallel work from this laboratory[11] suggests that the presence of a chronic productive cough in patients with asthma does not distinguish responders to ipratropium.

In conclusion, results of this study suggest that, contrary to some previous work in normal subjects[1 3] the action of ipratropium in patients with asthma is one of generalised bronchodilation of the tracheobronchial tree, but this conclusion is in agreement with other studies in normal subjects and in patients with chronic bronchitis.[4 10] Helioxygen MEFV curves do not give information which enable the response to ipratropium to be predicted.

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