Bronchial responsiveness to hyperventilation in children with asthma: inhibition by ipratropium bromide

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ABSTRACT Isocapnic hyperventilation dose response curves were constructed for 11 asthmatic children before and after pretreatment with placebo or ipratropium bromide, 40–1500 μg given by inhalation, on three separate days. The response before and after placebo was highly reproducible (within subject coefficient of variation 7.5%, 18%, and 22% for intervals of two hours, within two weeks, and over two weeks). It was independent of baseline lung function. Complete protection against hyperventilation induced asthma was achieved by ipratropium bromide 40 μg in six children and by 200 μg or more in a further four. The remaining child was unaffected by any dose of ipratropium up to 1500 μg . The dose of ipratropium required for protection was better related to the subjects' requirement for regular medication than to their sensitivity to hyperventilation or baseline lung function.

For over a decade exercise induced asthma has been a model of asthma by which the protective effect of drugs has been assessed in the laboratory. A single arbitrary level of exercise has often been used, coupled with a single dose of the drug under investigation. Moreover, in a group of asthmatic patients both baseline lung function and the level of bronchial responsiveness may vary widely, so not surprisingly the protection afforded by pretreatment with drugs has often seemed variable and the results conflicting.¹ All of these factors need to be taken into account to give useful information about the protective effect of drugs in laboratory models of acute asthma.

Deal and coworkers² suggested that airway cooling produced by the increase in minute ventilation was the stimulus for exercise induced asthma and recently hyperventilation has been used to assess airway responsiveness in asthmatic subjects. This permits a more easily controlled challenge in which the stimulus can be increased in a stepwise fashion, so that a dose-response relationship between minute

ventilation ($\dot{V}_E$) and airways obstruction can be demonstrated.³

The role of cholinergic mechanisms in exercise induced asthma is controversial,^{1,4,5} partly because of the limitations of single dose studies. Recently, Sheppard *et al*⁶ have suggested that the greater the bronchoconstrictor stimulus the greater the dose of anticholinergic drug (in their case atropine) that is required to provide protection. Most studies with anticholinergic drugs have been performed in adults with relatively mild asthma and the additional importance of variations in reactivity between individuals has not been adequately studied.

The aims of this study were, firstly, to look at the reproducibility of hyperventilation dose-response tests in asthmatic children with a wide spectrum of sensitivity to hyperventilation and, secondly, to investigate the effect of pretreatment with ipratropium bromide on hyperventilation induced asthma.

Methods

Seven boys and four girls with a history of exercise induced asthma were selected for the study (table 1). A wide range of severity of clinical asthma was represented in this group. Inhaled steroids and β agonists were discontinued for 12 hours and sus-

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Accepted 2 April 1984

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Table 1 Characteristics of the patients

Patient No	Sex	Age (y)	Height (cm)	Predicted FEV ₁ (l)	Usual treatment
1	M	10	135	1.9	B
2	M	9	138	2.1	B
3	F	8	139	2.2	CB
4	F	11	146	2.5	B
5	M	9	132	1.8	B
6	F	15	152	2.8	B
7	M	10	137	2.1	CB
8	F	16	145	2.4	SB
9	F	10	145	2.4	CB
10	M	13	161	3.2	TB
11	M	12	138	2.2	SB

B—inhaled bronchodilators; T—sustained release theophylline; S—inhaled corticosteroids; C—sodium cromoglycate.

tained release theophylline for 24 hours on each study day. Those children who were unable to stop medication through the night were given terbutaline SA 7.5 mg at 8pm on the night before each study day. Tests took place at the same time each day. The approval of the research ethics committee of Hammersmith Hospital was obtained.

HYPERVENTILATION TECHNIQUE

The tests were performed in an air conditioned laboratory. Resting FEV₁ was measured every 10 minutes until a stable baseline reading was obtained. The child then breathed at resting ventilation through a one way valve connected to a gas meter which was fed via a Douglas bag from a source of piped dry air (18–20°C). The first two minutes of hyperventilation then commenced, regulated as previously described using a calibrated motor driven pointer on the gas meter as a target.⁷ Carbon dioxide was added to the inspired air to keep the end tidal level constant. The actual minute ventilation rate was recorded, as was end tidal carbon dioxide concentration. The FEV₁ was measured (the best of two attempts being taken) 30 and 90 seconds and three minutes after the end of each period of hyperventilation. A stepwise increase in minute ventilation (VE)

of about 10 l min⁻¹ was made at five minute intervals. Repeated two minute periods of isocapnic hyperventilation, followed by FEV₁ measurements at 30, 90, and 180 seconds, were performed until there was a 20% fall in FEV₁. If the FEV₁ was still falling three minutes after the last hyperventilation step, it was recorded at two minute intervals until a rise was seen.

Dose-response curves were constructed by plotting FEV₁ against VE for each challenge test and the VE which caused a 20% fall in FEV₁ was calculated (PD₂₀: 1 min⁻¹). When, after premedication with ipratropium bromide, a child was able to reach the limits of voluntary ventilation during the test without a 20% fall in FEV₁ he was said to have been protected by the drug.

PROTOCOL

The subjects were tested on three days, the first two double blind (fig 1). A control test was carried out each day. Those in whom ipratropium bromide 200 µg blocked the response to hyperventilation were tested single blind on the third day after ipratropium 40 µg and again, if this was ineffective, two hours later with an additional 80 µg. Because of the prolonged action of ipratropium⁸ this latter dose rep-

Day 1 and 2 (all patients: random order)

HVDR $\xrightarrow{60 \text{ min}}$ $\xrightarrow{\text{Placebo or IB 200 } \mu\text{g}}$ $\xrightarrow{60 \text{ min}}$ HVDR

Day 3 (either (a) or (b): see text)

HVDR $\xrightarrow{60 \text{ min}}$ (a) IB 40 µg $\xrightarrow{60 \text{ min}}$ HVDR $\xrightarrow{60 \text{ min}}$ (a) IB 80 µg $\xrightarrow{60 \text{ min}}$ HVDR
HVDR $\xrightarrow{60 \text{ min}}$ (b) IB 500 µg $\xrightarrow{60 \text{ min}}$ HVDR $\xrightarrow{60 \text{ min}}$ (b) IB 1000 µg $\xrightarrow{60 \text{ min}}$ HVDR

Fig 1 Protocol used on the three study days. HVDR—hyperventilation dose-response study; IB—ipratropium bromide.

resented about 120 μg . Children who were not protected by 200 μg were tested on their third day after 500 μg followed two hours later by 1000 μg given by Wright's nebuliser (diluted with 2 ml normal saline), if a response to hyperventilation was still obtained. The concentration of a drug inhaled from a pressurised inhaler has been shown to be approximately equivalent to that from a nebuliser,⁹ so the total amount given was assessed as 1500 μg .

Placebo and ipratropium bromide at all concentrations, except the 1000 μg dose, were given from identical, specially prepared canisters; two puffs were administered in a standard way on each occasion except at the 500 μg dose, when five puffs were given. The children were unaware of the nature of the inhalations they were taking.

ANALYSIS OF DATA

Differences were assessed by a paired *t* test or by analysis of variance. The reproducibility of paired tests was assessed by using the standard deviations (SD) of the $\log_e$ ratios of the pairs, to obtain the coefficient of variation. The pooled SD, obtained by analysis of variance, was used to derive the coefficient of variation of tests repeated on several occasions.

Results were analysed with both actual PD_{20} and "normalised" PD_{20} , obtained by dividing by the predicted FEV_1 .

Results

REPRODUCIBILITY OF HYPERVENTILATION PD_{20}

On the placebo study day two hyperventilation tests were performed with a two hour interval (fig 2). The

Fig 2 Pairs of values of PD_{20} (the minute ventilation causing a 20% fall in FEV_1) from the two hyperventilation tests with a two hour interval on the placebo day.

mean values of PD_{20} for the two tests were close and the within subject coefficient of variation was 7.5% (95% confidence limit $\pm 15\%$). The within subject coefficient of variation increased as the test interval increased—to 18% for separate days within two weeks and 22% for an interval of over two weeks. The within subject coefficient of variation of

Table 2 Individual results*

Patient No	Control		IB 40 μg		IB 120 μg		Control		IB 200 μg		Control		IB 500 μg		IB 1500 μg	
	FEV_1	PD_{20}	FEV_1	PD_{20}	FEV_1	PD_{20}	FEV_1	PD_{20}	FEV_1	PD_{20}	FEV_1	PD_{20}	FEV_1	PD_{20}	FEV_1	PD_{20}
1	71	32	88	>38			89	35	100	>42						
2	80	28	88	>39			60	21	80	>37						
3	50	23	56	>29			38	23	43	>30						
4	89	27	98	>39			72	19	79	>36						
5	108	30	117	>39			97	30	103	>38						
6	100	15	117	>39			81	24	88	>36						
Mean (SD)	83	25	94	>37			72	25	82	>37						
	(19.1)	(5.6)	(20.7)	(3.7)			(19.5)	(5.5)	(19.7)	(3.5)						
7	77	21	95	36	95	37	43	25	52	>40						
8	86	15	94	27	86	27	57	23	95	>30						
9	63	30	65	30	63	32	67	38	76	>46						
Mean (SD)	75	22	85	31	81	32	56	29	74	>39						
	(9.5)	(6.2)	(13.9)	(3.7)	(13.4)	(4.1)	(9.8)	(6.6)	(17.6)	(6.6)						
10							56	27	72	37	64	34	86	40	94	>63
11							60	7	70	10	70	14	88	10	83	13
Mean for subjects 1-11							65	25	78	36						
							(17.3)	(7.8)	(18.3)	(10.6)						

* FEV_1 , % predicted; PD_{20} , l min^{-1} ; use of "greater than" (>) sign indicates that at the maximum level of ventilation achieved a 20% fall in FEV_1 had not occurred.

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baseline FEV₁ on separate days within two weeks was 14%. There was no correlation between variations in resting FEV₁ and PD₂₀ in control tests performed on different days, either within or between subjects, for actual (fig 3) or normalised PD₂₀.

EFFECT OF IPRATROPIUM BROMIDE ON HYPERVENTILATION PD₂₀

The effect of pretreatment of ipratropium bromide 200 µg was studied in all the children (table 2). There was a 20% mean rise in baseline FEV₁ after ipratropium, from a mean (SD) of 65% (17%) to 78% (18%) of the predicted value.¹⁰ A significant rise also occurred after placebo, from 70% (18%) to 74% (16%) predicted ($p < 0.01$) but this represented only a 6% mean rise.

Nine of the 11 subjects (nos 1–9) were protected by ipratropium bromide 200 µg. In these children there was a fall in FEV₁ after hyperventilation of less than 10% despite a 27% increase in the mean (SD) level of the hyperventilation stimulus to 37 (5.2) l min⁻¹, compared with the maximum control V_E of 27 (6.5) l min⁻¹. Six children (1–6) were found to be protected by ipratropium 40 µg and in the remaining three (7–9) there was some shift in the dose-response curve after 40 µg but the addition of a further 80 µg, giving an approximate total of 120 µg, did not afford any greater protection (table 2).

The two children (10 and 11) who were not protected by pretreatment with ipratropium bromide 200 µg were tested with the higher concentrations. Subject 10 showed a progressive shift in his dose-response curve as the concentration of ipratropium was increased from 200 to 500 µg, with complete protection after 1500 µg (fig 4). The most sensitive subject, No 11, failed to show any protection from hyperventilation induced asthma at any dose used.

Fig 3 Relationship of PD₂₀ (see figure 2 legend) and

Fig 4 Dose-response curves of subject 10 showing pretreatment dose of ipratropium bromide in µg. There were two study days, indicated by the continuous and dotted lines.

No significant correlation was found between sensitivity to hyperventilation (PD₂₀) and the dose of ipratropium bromide required to afford complete protection. The usual treatment being taken by the children was significantly associated with the dose of ipratropium required for protection. Of the six children protected by ipratropium 40 µg, five were taking intermittent bronchodilators only; of the children requiring 200 µg or more, all required regular prophylactic treatment (Fisher's exact test, $p < 0.02$).

Discussion

Isocapnic hyperventilation challenge tests were easily performed in our group of 11 children, and provided reproducible values of PD₂₀. The degree of reproducibility of the PD₂₀, calculated from tests performed with a two hour interval (coefficient of variation 7.5%), makes the test useful for assessing the protective effect of drugs. The reproducibility compares favourably with that of histamine inhalation challenge,¹¹ which has been successfully used as a sensitive means of detecting changes in bronchial responsiveness.^{12 13}

The between test reproducibility considerably decreased when tests were performed on separate days, giving a coefficient of variation of 18%, increasing to 22% when the test interval exceeded two weeks. O'Byrne and colleagues,¹⁴ using sub-freezing air and expressing the stimulus as respiratory heat exchange, showed a similar coefficient of variation of 21% when the interval between tests

on each study day is advisable if information about the protective effect of a drug in individual subjects is required, or if the group numbers are small. The results from this present study show that without control challenges on each day the variation could have given a false impression about the protective effect of drugs in individual cases (table 2). It was considered wise to perform a pair of tests with at least a two hour interval between them, as refractoriness has been found to occur in some children after hyperventilation induced asthma.^{15, 16} Refractoriness could have had a flattening effect on individual dose-response curves, but this did not interfere with the reproducibility of the test.

We found considerable intersubject difference in the dose of ipratropium bromide required to blunt or abolish the fall in FEV₁ after hyperventilation. Six children were completely protected by 40 µg but four required 200–1500 µg and one was unaffected by 1500 µg. We do not know whether a higher dose would have protected this latter child, although even at this dose there were no ill effects and no change in pulse rate. The reproducibility of the protective effect of ipratropium has never been assessed. In a study¹⁵ looking at the effect of ipratropium on single dose hyperventilation challenge we found 11 of 19 subjects were completely protected by ipratropium bromide 80 µg, and it was suggested that a cholinergic mechanism was important only in those subjects whom we were unable to make refractory by repeated challenges. Further work is needed to see whether those subjects requiring higher doses of ipratropium to prevent hyperventilation induced asthma are more refractory to repeated hyperventilation than those protected by lower doses.

Protection by a bronchodilator drug against induced asthma could be explained by an increase in airway calibre. The measurement of FEV₁ (or any other parameter of airflow) is only an approximate and indirect measure of airway calibre. We found no evidence, however, that changes in baseline FEV₁ were associated with changes in PD₂₀ (fig 3). Spontaneous changes in FEV₁ before control tests on two separate test days (table 2) had no effect on PD₂₀, whereas after ipratropium bromide 200 µg similar changes in FEV₁ were associated with a considerable and highly significant increase in PD₂₀ (fig 5). The mean PD₂₀ value after ipratropium bromide 200 µg was in fact an underestimate, since nine out of 11 children were completely protected (that is, achieved their maximum $\dot{V}_E$ without a fall in FEV₁); so the maximum $\dot{V}_E$ achieved was used in place of the PD₂₀ for these children. Thus only a small part of the protection against hyperventilation induced asthma afforded by ipratropium bromide was due to bronchodilatation, as others have recently

reported.¹⁷ The PD₂₀ as an index of sensitivity to hyperventilation was not a useful predictor of the dose of ipratropium bromide needed to afford complete protection. Although some children who were least responsive to hyperventilation were protected by lower doses of ipratropium, two individuals (3 and 6) were highly sensitive to hyperventilation but were fully protected by ipratropium 40 µg. PD₂₀ values in subjects of differing size are not strictly comparable; nevertheless, normalising for size failed to improve the relationship between control PD₂₀ and the protective effect of ipratropium. Sheppard *et al*⁶ did find that their more responsive subjects required higher concentrations of inhaled atropine to prevent the effect of cold air hyperventilation. In the present study the usual treatment taken by the subjects was a better guide to their sensitivity to ipratropium.

Hyperventilation induced asthma is said to be equivalent to exercise induced asthma.⁷ Numerous studies looking at the protective effects of anticholinergic drugs in exercise induced asthma have shown conflicting results.^{1, 4, 5, 18} These discrepancies are probably accounted for by the use of a single level of exercise (that is, a challenge test comprising a single stimulus) and by differences between studies both in drug dose and in the responsiveness of the subjects. Although a stimulus-response relationship to exercise can be found,⁴ in practice it is so cumbersome as to be impractical. In contrast, the hyperventilation stimulus-response study is easily performed and even children with highly labile airways can be safely tested. Subfreezing air, a very potent stimulus,

Fig 5 Variation in PD₂₀ (see figure 2 legend) after spontaneous change in FEV₁ between two control tests on day 1 and day 2 (solid circles), compared with change in PD₂₀ before and after ipratropium bromide (IB) 200 µg (open circles): means and standard errors for all 11 subjects. Solid circles represent the mean value derived from each subject's best and worst FEV₁ on the two control days; open circles represent the change in FEV₁ induced by the bronchodilator effect of ipratropium 200 µg.

could be dangerous for patients as severely affected as ours.

By the use of hyperventilation dose-response challenge tests and of varying doses of ipratropium bromide, we have shown a range of responsiveness of asthmatic children to the drug, which was independent of the severity of hyperventilation induced asthma and of the bronchodilator action of ipratropium, but which did related to the overall clinical severity of asthma. A "standard" dose for all asthmatic children is clearly inappropriate. Moreover, a dose which produces effective bronchodilatation may be quite inadequate to protect against a powerful provoking stimulus, just as a dose failing to produce bronchodilatation may protect fully. Much higher single doses of ipratropium bromide than are normally recommended may be given to individual patients with particularly intractable asthma and in this study they produced no side effects.

We are grateful to the Asthma Research Council and to Boehringer Ingelheim for financial support.

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