Upsala J Med Sci 93: 71–80, 1988

Lack of Correlation between the Grade of Methacholine-induced Bronchial Hyperreactivity and Ipratropium Bronchodilation in Asthmatics

Hans Hedenström and Thomas Wegener

Departments of Clinical Physiology and Lung Medicine, Uppsala University, Akademiska sjukhuset, Uppsala, Sweden

ABSTRACT

In 46 never-smoking randomly chosen patients with non-allergic asthma, 40 to 60 years old, a methacholine hyperreactivity test and lung function tests were performed after inhalation of different doses of ipratropium bromide (IB). The grade of hyperreactivity was measured as the cumulative dose of methacholine necessary to produce a decrease in the forced expiratory volume in one second of 20% of the lowest post-NaCl value (PD20). The following lung function tests were carried out: Lung volumes, ventilatory capacity including flow-volume curves, airway resistance and nitrogen single-breath wash-out test. The bronchodilator effect, measured as a change in the different lung function tests for different doses of IB given (0.08 mg, 0.15 mg and 0.25 mg), was correlated to the grade of hyperreactivity (PD20 dose). No or only a slight correlation was found between the grade of methacholine-induced hyperreactivity and the bronchodilator effects of the different doses of IB. These results indicate a lack of correlation between an anticholinergic bronchodilator effect and the grade of methacholine-induced bronchial hyperreactivity, or possibly an insensitivity of the above-mentioned methacholine test.

INTRODUCTION

Ipratropium bromide (IB) is a quaternary isopropyl derivative of the muscarinic antagonist atropine. It is poorly absorbed into the blood stream because of its quaternary nature and thus has minimal cardiovascular side effects. The mode of action of IB is via blockade of the cholinergic system in the bronchial tree, thus causing bronchodilatation when administrated by a metered dose inhaler (MDI) or by nebulized inhalation (NI).

The preventive effect of anticholinergic drugs on bronchial hyperreactivity - measured as bronchial asthma induced by exercise or cold air - is a matter of debate, although it is usually reported to be poor or variable (2, 3, 4, 5, 12, 13, 15, 16). Kraan et al (10), in an investigation of patients suffering from allergic bronchial asthma, compared the effects of budesonide and terbutaline on the bronchial hyperreactivity as assessed by inhalation provocation tests with histamine and propanolol. They concluded that this hyperreactivity was improved by budesonide, but was temporarily increased following treatment with terbutaline. Sheppard et al (14) reported that inhaled atropine sulphate totally blocked cold air-induced bronchial asthma, but found that the doses needed were much higher than those required to relieve the resting bronchomotor tone or to block methacholine-induced bronchoconstriction. Poppius et al (13) treated patients with mild bronchial asthma with IB in doses 20-50 times higher than those known to have a marked effect on the resting bronchomotor tone in clinically stable bronchial asthma, and found that this treatment had no blunding effect on the bronchoconstrictive response to breathing of cold air during exercise.

The aim of the present study was to determine whether there is a correlation between the grade of hyperreactivity and the dose-response bronchodilator effect of the anticholinergic drug IB, measured in terms of lung volumes, airway resistance, ventilatory capacity and nitrogen single-breath wash-out in moderate non-allergic bronchial asthma.

SUBJECTS AND METHODS

SUBJECTS: Lung function tests were performed in 46 patients (22 males and 24 females) with symptoms and signs of moderate non-allergic bronchial asthma of more than two years' duration, selected on the basis of their clinical history. Their mean age was 50 years (range 40 - 60). They were all never-smokers, had a normal serum IgE level, and a negative skin test (with a standard panel of 12 allergens). When there was a discrepancy between the clinical history and skin test, RAST was performed. None of the patients were receiving oral steroid treatment. Bronchodilator tablets were not allowed later than 10 hours before the test.

METHACHOLINE TEST: The patients first inhaled 0.5 ml of NaCl delivered from a De Vilbiss-40 nebulizer, and then 0.5 ml of methacholine solution in doubling concentrations at 3-minute intervals, from 0.125 to 20 mg/ml until the forced expiratory volume in one second (FEV1) had decreased to below 80% of the lowest post-NaCl value or until the highest concentration of methacholine had been given. The cumulative doses of methacholine necessary to produce a decrease in FEV1 of 20% of the lowest post-NaCl value (PD20) were obtained from the log-dose response curve by linear interpolation of the last two points (1, 11).

LUNG FUNCTION TESTS: The following lung function tests were performed: static lung volumes, measurement of airway resistance, dynamic spirometry, including registration of flow-volume curves, and the nitrogen single-breath test.

The total lung capacity, functional residual capacity and residual volume, together with airway resistance and volumic airway conductance, were measured in a Siemens body plethysmograph of constant volume type. Dynamic spirometric investigations were carried out with a dry rolling seal spirometer. The dynamic spirometry included measurement of vital capacity, forced vital capacity, FEV1, FEV1 in per cent of the vital capacity or total

lung capacity, measurement of maximal voluntary ventilation at a respiratory rate of 40 breaths per minute, and registration of flow-volume curves. From the maximal expiratory flow-volume curve, the peak expiratory flow and flows at 75%, 50% and 25% of the forced vital capacity and at 70% and 60% of the total lung capacity were obtained. From the nitrogen single-breath test, the slope of the alveolar plateau and the closing volume and closing capacity were determined.

After the lung function tests the patient was randomly allotted to one of three groups, and inhaled 0.08 mg, 0.15 mg or 0.25 mg of the anticholinergic drug ipratropium bromide (Atrovent®, Boehringer-Ingelheim, FRG) in 2.5 ml of NaCl from a nebulizer (Pari Inhalier Boy) during a period of 15 minutes. One hour after the administration of the drug, the lung function tests were repeated. The number of patients and the mean ages of the different dose groups are presented in Table 1. The pulmonary function tests and the criteria for acceptable measurements and for selecting values from multiple recordings are described elsewhere (7, 8, 9).

RESULTS

All values from the lung function tests were expressed as residuals from the predicted values, using prediction formulas which take into account the effect of age and body size (7, 8). The results of the methacholine test showed a skewed distribution for the PD20 dose between 0.125 and 20 mg/ml, where most patients had a value below 3.0 mg/ml (Figure 1). A logarithmic transformation was therefore applied to give a normal distribution. The Pearson correlation test was performed both for the original and for the logarithmic PD20 data.

There was no correlation between the PD20 dose of methacholine and the effect of IB on lung volumes. The bronchodilator effect, measured as increased volumic airway conductance, showed a slight significant correlation ($p<0.05$) for the IB doses 0.08 and 0.15 mg. In addition, a slight correlation ($p>0.05$) was found between the PD20 dose and increasing maximal expiratory flow and a decreasing slope of the alveolar plateau for 0.08 mg of IB. However, for most lung function tests the bronchodilator effect of IB showed no statistically significant correlation with the measured PD20 dose or with this dose after the logarithmic transformation of the PD20 data.

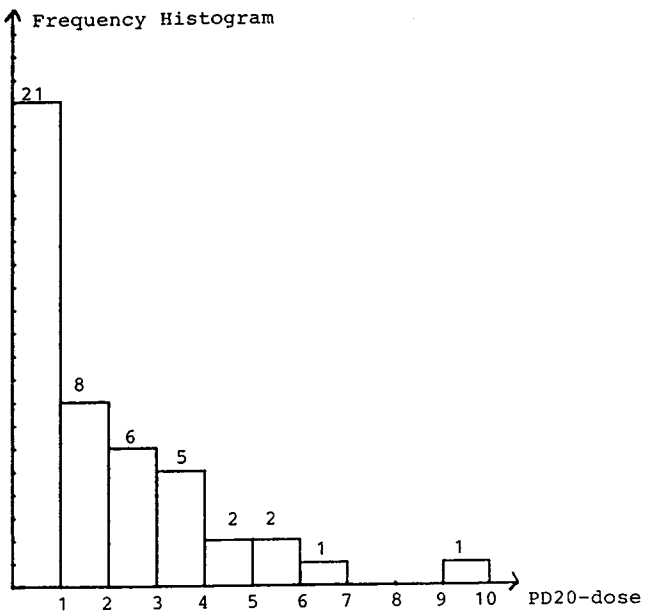

Fig 1. The frequency distribution of the cumulative doses of methacholine necessary to produce a decrease in FEV1 of 20% of the lowest post-NaCl value (PD20).

Table 1.

Correlation coefficients between the logarithm of the methacholine test and the effects of tree different doses of ipratropium bromide on different lung function tests. (All values are non-significant except those marked with an asterisk (*) which means a significance level of less than 0.05)

	Dose of ipratropium bromide		
	0.08 mg (n=14)	0.15 mg (n=15)	0.25 mg (n=17)
Lung volumes			
Total lung capacity	-0.13	-0.09	-0.05
Vital capacity	-0.36	-0.30	-0.16
Airway Resistance			
Volumic airway conductance	-0.48*	-0.42*	-0.28
Ventilatory Capacity			
Forced expiratory volume in one second	-0.14	-0.05	-0.08
Maximal expiratory flow	-0.57*	-0.33*	-0.28
Forced expiratory flow at 60% of total lung capacity	-0.54*	-0.42*	-0.37
Nitrogen wash-out test			
Slope of alveolar plateau	+0.48*	+0.36	+0.54*
Closing volume	+0.12	+0.14	+0.27
Closing capacity	+0.12	+0.03	+0.21

DISCUSSION

Trials have previously been made to investigate the influence of several anti-asthmatic drugs on the bronchial hyperreactivity in both non-allergic and allergic bronchial asthma.

Hegardt et al (6) studied the influence of long-term inhaled terbutaline on basal bronchial hyperreactivity and evaluated the

possibility that beta-2-agonists (terbutaline) could change the bronchial hyperreactivity in symptom-free allergic asthma. They concluded from their results that four weeks of treatment with terbutaline did not alter the basal bronchial hyperreactivity in patients with allergic asthma. Kraan et al (10) compared the effects of budesonide and terbutaline on bronchial hyperreactivity. They reported that the bronchial hyperreactivity was improved by budesonide possibly by a dampening of late allergic reactions, but that it was temporarily aggravated by treatment with terbutaline.

In 13 patients with allergic asthma, Thomson et al (16) investigated the effects of placebo, sodium cromoglycate (SC), IB and IB+SC to assess their inhibitory action in exercise-induced asthma (EIA). In eight of the patients SC, IB and IB+SC significantly inhibited the percentage fall in FEV1. In five patients IB had no preventive action, unlike SC and IB+SC. It was therefore postulated that mediator release is an important factor in the development of exercise-induced asthma in most allergic asthmatics, whereas cholinergic mechanisms are less relevant.

Poppius et al (13) evaluated the preventive effect of inhaled ipratropium powder on low-grade bronchoconstriction elicited by breathing cold air during exercise in ten adult patients with mild non-allergic or allergic bronchial asthma. They concluded that doses of ipratropium up to 50 times higher than those known to have a marked effect on the resting bronchomotor tone in clinically stable asthma did not blunt the bronchoconstriction following exercise with cold air breathing. On the contrary, Sheppard et al (14) found that IB inhalation had a protective effect against bronchial asthma induced by cold air.

Plausible explanation for these findings are proposed by Poppius et al (13), for exemple that the median diameter of the particles generated by the de Villbiss nebulizer are probably smaller than those of the ipratropium powder, and thus penetrate further down into the bronchial tree to the peripheral airways. Wegener & Hedenström (17, 18) have found that IB has an effect on small

airways supporting both the explanation by Poppius et al (13) and the protective effect reported by Sheppard et al (14). However, the results of the present study failed to show any correlation between the grade of hyperreactivity (PD20) and the bronchodilator effect of IB in doses of 0.08, 0.15 and 0.25 mg. It might be expected that patients with a high grade of methacholine-induced bronchial hyperreactivity will respond better to increasing doses of IB than those with a low grade of hyperreactivity. Another plausible explanations might be that the methacholine test and the lung function tests could not be performed on the same day. Climatic changes (cold air, humidity), drug intake, negative environmental effects and other factors uncontrolled in this study might also explain the lack of correlation. For the purpose of the present investigation the hyperreactivity test used, with methacholine, could be too insensitive to get a precise measurement of the grade of hyperreactivity although this type of hyperreactivity test has been found adequate in other investigations (1, 11).

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Mrs Maud Marsden for linguistic revision and the financial support from the Swedish National Association against Heart and Chest Diseases and the Bror Hjerpstedt Foundation.

REFERENCES

1. Cockcroft, D.V., Killian, D.N., Mellon, J.J.A. & Hargreave, F.E.: Bronchial reactivity to inhaled histamine. A method and Clinical survey. Clin Allergy 7:235-243, 1977.

2. Godfrey, S.: Exercise-induced asthma application to clinical trials (Proceedings Br J Dis Chest 71:232-233, 1977.

3. Griffin M.P., Fung K.F., Ingram R.H J:r & McFadden E.R. Jr. Dose-response effects of atropine on thermal stimulus response relationships in asthma. J Appl Physiol 53:1576-1582, 1982.

4. Hartley J.P.R. & Davies B.H. Cholinergic blockade in the prevention of exercise-induced asthma. Thorax 35:680-685, 1980.

5. Heaton R.W., Henderson A.F., Gray B.J. & Costello J.F. The bronchial response to cold air challenge: evidence for different mechanisms in normal and asthmatic subjects. Thorax 38:506-511, 1983.

6. Hegardt B., Löwhagen O., Rak S. & Svedmyr N. Influence of long-term inhaled terbutaline on basal bronchial hyperreactivity. Annual meeting of the European academy of allergology and clinical immunology. Stockholm 1985, abstract 202.

7. Hedenström, H., Malmberg, P. & Agarwal, K.: Reference values for lung function tests in females. Regression equations with smoking variables. Bull Eur Physiopathol Respir 21:551-557, 1985.

8. Hedenström, H., Malmberg, P. & Fridriksson, H.V.: Reference values for lung function tests in men. Regression equations with smoking variables. Uppsala J Med Sci 91:299-310, 1986.

9. Hedenström, H. & Malmberg, P.: Utility of relating pulmonary air flow measures to total lung capacity. Bull Eur Physiopathol Respir 22: 559-564, 1986.

10. Kraan J., Koeter G.H. v.d. Mark Th. W., Sluiter H.J. & de Vries, K. Changes in bronchial hyperreactivity induced by 4 weeks of treatment with antiasthmatic drugs in patients with allergic asthma: A comparison between budesonide and terbutaline. J Allergy Clin Immunol 76: 628-636, 1985.

11. Machado, L.: Increased bronchial hypersensitivity after early and late bronchial reactions provoked by allergen inhalation. Allergy 40:580-585, 1985.

12. Pakes G.E. Brogden R.n., Heel R.C. Speight, T.M. & Avery G.S. Ipratropium bromide: a review of its pharmacological properties and therapeutic efficiacy in asthma and chronic bronchitis. Drugs 20: 237-324, 1980.

13. Poppius H., Sovijärvi A.R.A. & Tammilehto L. Lack of protective effect of high-dose ipratropium on bronchoconstriction following exercise with cold air breathing in patients with mild asthma. Eur J Resp Dis 68: 319-325, 1986.

14. Sheppard D., Epstein J. Holtzman M.J., Nadel J.A. & Boushey H.A. Dose dependent inhibition of cold air induced bronchoconstriction by atropine. J Appl Physiol 53: 169-174, 1982.

15. Simonsson, B.G., Skoog B.E. & Ekström-Jodahl B. Exercise induced airways constriction. Thorax 27: 169-180, 1972.

16. Thomson N.C., Patel K.R. & Kerr J.W. Sodium cromoglycate and ipratropium bromide in exercise induced asthma. Thorax 33: 694-699, 1978.

17. Wegener, T. & Hedenström, H.: Anticholinergic bronchodilatation in nonallergic bronchial asthma, Prog Resp Res, vol 19: 344-347, 1985.

18. Wegener, T. & Hedenström, H.: Effect of nebulized ipratropium bromide on lung function in nonallergic bronchial asthma. Respiration in Press.

Adress for reprints:

Hans Hedenström
Department of Clinical Physiology
University Hospital
751 85 Uppsala
Sweden