

Bronchodilating effect of ipratropium bromide inhalation powder and aerosol in children and adolescents with stable bronchial asthma

Ulrik CS, Backer V, Bach-Mortensen N. Bronchodilating effect of ipratropium bromide inhalation powder and aerosol in children and adolescents with stable bronchial asthma. *Allergy* 1992; 47: 133–137.

The purpose of this study was to compare the bronchodilating effect of ipratropium bromide (IB) administered by a conventional Ingelheim powder device system (IPI) and by a metered dose inhaler (MDI) in children and adolescents with stable bronchial asthma. Seventy patients, aged 7 to 16 years, with stable bronchial asthma from our outpatient clinic were tested for bronchial responsiveness to inhaled IB. Fifteen (21%) of the 70 subjects were found to have a substantial bronchial response to inhalation of 40 µg IB, i.e. at least 15% increase in FEV₁ 30 min after inhalation; the remaining 55 subjects had <15% increase in FEV₁. No relationship between severity of asthma, age or sex and bronchial responsiveness to inhaled IB was found. Among the 15 subjects who had substantial bronchial response to IB, the increase in FEV₁ after inhalation of fenoterol tended to be greater than the response to inhaled IB, although this did not reach statistical significance. Responders, i.e. subjects who had at least 15% increase in FEV₁ after inhalation of IB, took part in a double-blind, cross-over study of the bronchodilating effect of 40 µg IB delivered by IPI and MDI. We found no significant differences in the bronchodilating effect during a 6-h follow-up. Maximum bronchodilating effect of IB was reached after 30 min and the maximum response lasted for 90 min. No side or adverse effects were observed following inhalation of IB. We conclude that before starting treatment with ipratropium bromide for bronchial asthma in children and adolescents, the patients should be tested for bronchial responsiveness to inhaled IB to find out whether they are responders or nonresponders; and further that, among responders, inhalation of powder is as effective as inhalation from a dosi-aerosol.

Clinical aspects

On the basis of the findings in the present study, we conclude that before starting treatment with ipratropium bromide (IB) for bronchial asthma in children and adolescents the patients should be tested for bronchial responsiveness to inhaled IB in order to find out whether they are responders or nonresponders; and further that, among responders, inhalation of powder is as effective as inhalation from a dosi-aerosol.

C. S. Ulrik¹, V. Backer¹,
N. Bach-Mortensen²

¹ Laboratory of Respiratory Physiology, Department of Medicine B, and ² Department of Paediatrics GKG, State University Hospital, Copenhagen, Denmark

Key words: bronchial asthma; children; ipratropium bromide.

Charlotte Ulrik
Dept. of Clinical Physiology &
Nuclear Medicine KF-4011
Rigshospitalet
Blegdamsvej 9
DK-2100 Copenhagen Ø
Denmark

Accepted for publication 9 July 1991

In bronchial asthma, the airways are found to respond to a variety of pharmacologic agents, e.g. β_2 -agonists and atropine; part of this responsiveness is thought to be caused by stimulation of the autonomic nervous system. Several pharmacologic actions of adrenergic agonists are important in the treatment of asthma, and the best characterized

bronchodilator action of the adrenergic agonists on airways is relaxation of airway smooth muscle. However, for many years it has been known that asthma can also be treated with muscarinic antagonists, e.g. ipratropium bromide (IB), because they can effectively block the contraction of airway smooth muscle and the increase in secretion of mucus that oc-

curs in response to vagal activity (12). Some investigators have found IB to be an effective alternative for treatment of mild acute asthma in children (7, 14, 15, 22). IB permits delivery of high doses to the muscarinic receptors in the airways because the compound is poorly absorbed and does not readily enter the central nervous system, and has therefore only few side effects (13); and further, it can be used in infants with bronchoconstriction (10). Studies with this agent have shown that the degree of involvement of parasympathetic pathways in bronchomotor responses varies among adults with bronchial asthma (8); in some, bronchoconstriction is inhibited effectively, whereas in others, bronchoconstriction is inhibited only modestly (2). That administration of higher doses of the muscarinic antagonists fails to inhibit the response further implies that mechanisms other than parasympathetic reflex pathways must be involved (2, 12).

IB can be inhaled either as powder or as aerosol. Inhalation of powder is preferable because it is more likely to be inhaled with an optimal technique, even in children at the age of 3 to 4 years (1, 18); whereas inhalation from an aerosol is more difficult (6, 19); also, dosis-aerosols contain freon. The purpose of this study was to compare the bronchodilating effect of IB administered by a powder device system and by a metered-dose inhaler in children and adolescents with stable asthma.

Material and methods

Material

The present study consisted of two parts:

Part 1 (inclusion phase). A total of 70 children and adolescents, median age 13 years (range 7–16), with stable bronchial asthma, i.e. unchanged anti-asthmatic medication for at least 4 weeks and no need for systemic steroids within the last 12 weeks, were tested for bronchial response to 40 µg of IB inhaled from a conventional Ingelheim powder device system (IPI). All subjects regularly attended the outpatient clinic at the Department of Pediatrics at the University Hospital in Copenhagen, and had previously been shown to have reversible airways obstruction (FEV_1 increased 15% or more after bronchodilator inhalation); all participating subjects had a baseline FEV_1 within the normal range (26).

Subjects, who had at least 15% increase in FEV_1 30 min after inhalation of 40 µg of IB, were included in the second part of this study (the investigational trial).

Part 2 (investigational trial). The investigational trial was a double blind, randomized, cross over study of the bronchodilating effect of 40 µg of IB inhaled ei-

ther from an IPI or a metered dose inhaler (MDI) during a 6-h follow-up. Fifteen, median age 12 years (range 7–16), of the 70 subjects tested could be included in this part of the study, one of the 15 responders was not willing to terminate the study.

The study was approved by the ethics committee of Copenhagen and informed consent was obtained from all participating subjects and their parents.

Methods

Part 1. All participating subjects had a baseline lung function test, measured with a pneumotachograph (Vitalograph®). All subjects were asked not to take theophylline for at least 24 h, oral β_2 -agonist for 18 h, and not to use inhaled bronchodilators for 6 h before testing. Inhaled steroids were continued, if used. The baseline lung function tests included measurements of FEV_1 , FVC, VC, FEF_{50} and FEF_{25} . The highest of three technically acceptable measurements was used for data analysis. Baseline lung function testing was followed by a reversibility test; FEV_1 was measured at 0, 15 and 30 min after inhalation of 40 µg of IB, delivered by an IPI. Bronchial response was calculated as follows: $(FEV_{1\text{after}} - FEV_{1\text{baseline}}) / FEV_{1\text{baseline}}$. Subjects, who had <1% increase in FEV_1 after inhalation of IB ($n = 36$) were excluded from further examination; whereas all subjects who had an increase in FEV_1 of >1%, but <15% were tested once more with IB.

Part 2. All subjects, who fulfilled the following criteria: 1) >15% increase in FEV_1 30 min after inhalation of 40 µg IB (powder, IPI system), 2) <15% decrease in FEV_1 after inhalation of a freon aerosol (placebo-aerosol) and 3) >15% increase in FEV_1 15 min after inhalation of 0.2 mg fenoterol (tested on a separate day), (powder, IPI system), were included for further examination. The investigational trial, powder versus dosis-aerosol, was performed on 2 separate days, less than a week apart (median 1 day, range 1–5 days), from 8 a.m. to 3 p.m.

On one day IB was delivered by an IPI and placebo by a MDI, and the second day visa versa. FEV_1 was measured prior to inhalation of IB and after 15, 30, 60, 120, 180, 240, 300 and 360 min. At the end of each day all subjects had their FEV_1 measured 15 min after inhalation of 0.2 mg fenoterol (IPI system).

Data analysis. Predicted values for FEV_1 , FVC, VC, FEF_{50} and FEF_{25} were calculated according to Zapletal (26). The Mann-Whitney rank sum test was used for comparing groups. The Friedmann test was used to analyse changes in lung function over time.

Results

When the patients had their first test for bronchial response to inhaled IB, we found that 7 (10%) had at least 15% increase in FEV₁, whereas 36 (51%) had unchanged FEV₁ ($\leq 1\%$) 30 min after inhalation of 40 µg of IB (Group 0). Twenty-seven (39%) patients had an increase in FEV₁ of $> 1\%$, but $< 15\%$, and they therefore had another reversibility test with IB (Table 1). At this second test, another 8 subjects were found to have substantial (i.e. $\geq 15\%$) increase in FEV₁ after inhalation of IB; whereas 19 subjects still only had a minor bronchial response to inhaled IB (Group 1, $n = 19$). This means that among 70 children and adolescents with stable asthma, who earlier had shown a 15% or greater improvement in FEV₁ after inhalation of a standard dose of β_2 -agonist, only 15 (21%) patients were found to have an increase in FEV₁ of at least 15% after inhalation of 40 µg of ipratropium bromide (Group 2, responders), (Table 1).

No differences in either sex, age or asthmatic symptoms were found between the 15 responders (Group 2) and the 55 nonresponders. No difference in baseline FEV₁, expressed as percent of predicted value (% pred.), was found between the 36 subjects (Group 0) (103% pred.) and the 19 subjects in Group 1 (95% pred.), ($p = 0.08$). As shown in Table 2, the 8 subjects, who only at the second test with IB had significant increase in FEV₁, were found to have significantly more reduced baseline FEV₁ (76% pred.) than the 19 subjects in Group 1 (95% pred.), ($P = 0.01$). In general, no significant differences in lung function were found between the subjects in Groups 1 and 2; however, baseline FEF₂₅ was found to be significantly more reduced among subjects in Group 2 (median 59% pred.), than among the subjects in Group 1 (median 65% pred., $p = 0.02$).

The bronchial response to inhalation of placebo was significantly lower than the response to both IB

Table 2. Subjects in Group 2 ($n = 15$) divided according to their initial response to inhaled ipratropium bromide

	Group 2		
	neg	pos	
	$n = 8$ 1	$n = 8$ 1	$n = 7$ 2
VC	98.7	85.0	102.1
FEV ₁	89.6	75.5	90.5

(1: subjects ($n = 8$) who were tested twice with ipratropium bromide, and only had significant increase in FEV₁ at the second test); (2: subjects ($n = 7$), who had significant response ($> 15\%$) to IB at the first test).

Table 3. Increase in FEV₁ after inhalation of ipratropium bromide (IPI), placebo aerosol (placebo) and fenoterol powder (BETA) ($n = 14$)

	Median change of FEV ₁		
	IPI	placebo	BETA
Lung function test			
15 min	12.2	4.3*	18.6
30 min	16.2	2.8**	20.9

* $p < 0.05$ and ** $p < 0.01$ (Mann-Whitney test).

and fenoterol ($p < 0.01$) (Table 3). The increase in FEV₁ tended to be greater after inhalation of fenoterol than after inhalation of IB (Table 3), although this did not reach statistical significance.

Of the 14 patients who entered the investigation trial, 3 were girls, 2 had a negative skin prick test to 9 common aero-allergens, and according to the level of bronchial hyperresponsiveness the 14 subjects had mild to moderate asthma (median PC₂₀, histamine 1.4 mg/ml, range 0.3–7.0).

For the patients in Group 2 ($n = 14$) no significant differences in baseline FEV₁ were found between the days of inclusion (82% pred. and 83% pred., respectively) or between the 2 days of trial (99% pred. and 94% pred., respectively); however, baseline FEV₁ was found to be significantly lower on the days of inclusion than on the days of trial (83% pred. and 99% pred., respectively, $p < 0.01$).

As shown in Fig. 1, the maximum increase in FEV₁ % pred. was reached 30 min after inhalation of IB, and the maximum response lasted 90 min, whereafter lung function began decreasing towards baseline values. IB inhaled from a dosi-aerosol seems to reveal less bronchodilation, although the difference did not reach statistical significance (Table 4). The increase in FEV₁ 15 min after inhalation of 0.2 mg fenoterol at the end of the 2 days of trial was rather poor (Fig. 1).

No side or adverse effects were noted after inhalation of ipratropium bromide or fenoterol, nor had

Table 1. Baseline lung function test (% predicted) in 19 asthmatic subjects (Group 1) with insignificant bronchial response to ipratropium bromide and 14 asthmatic subjects (Group 2) with at least 15% increase in FEV₁ after inhalation of ipratropium bromide

	Group 1 ($n = 19$)		Group 2 ($n = 14$)			
	Part 1		Part 1		Part 2	
	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2
VC	97.6	95.0	93.7	99.1	104.3	104.9
FVC	96.8	96.4	92.5	98.5	105.9	108.6
FEV ₁	94.5	97.6	82.0	83.0	98.6	93.5*
FEV ₁ /FVC	77.0	76.5	75.2	74.6	74.0	71.0
FEF ₅₀	74.9	75.8	54.6	60.5	61.4	62.4
FEF ₂₅	62.8	78.0	36.7	38.1	41.3	34.5

* $p < 0.05$ (Friedmann test). Values adjusted to BTPS.

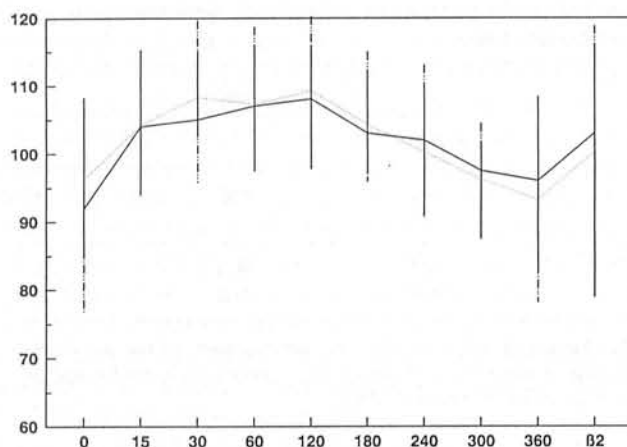


Fig. 1. Changes over time (minutes, abscissa) in FEV₁ % predicted (ordinate) after inhalation of ipratropium bromide either as powder (solid line) or as aerosol (chain, dotted line), and 15 min after inhalation of fenoterol.

Table 4. Change in FEV₁ % pred. after inhalation of 40 µg ipratropium bromide delivered by a powder device system (IPI) and a metered dose inhaler (MDI), (*n* = 14)

	Median change in FEV ₁ %pred.	
	IPI	MDI
Lung function test		
15 min	12.2	5.1
30 min	16.2	11.2

any subject in this study decrease in FEV₁ after inhalation of either of the 2 bronchodilators.

Discussion

The purpose of this study was to compare the bronchodilating effect of ipratropium bromide inhalation powder and aerosol in children and adolescents with stable bronchial asthma. In the treatment of acute asthma, ipratropium bromide has been found to be as efficient as β_2 -agonists, or only slightly less so (7, 23, 24). This study showed that only 15 (21%) of 70 children and adolescents with bronchial asthma had substantial increase in FEV₁ 30 min after inhalation of 40 µg of ipratropium bromide. However, the subjects in this study were clinically stable and had a baseline lung function within the normal range (26), and it is possible that a different result may have been found in children and adolescents with reduced lung function and/or unstable asthma. This suggestion is supported by our finding that 8 of the subjects only had significant bronchial response to ipratropium bromide when they were re-tested on a day where they had reduced baseline lung function. Petrie (20) and Ruffin (21) have shown that in mild asthma there is little advantage from adding ipra-

tropium bromide to salbutamol; whereas patients with more severe asthma may benefit from both drugs because there may be reduced β -adrenoceptor function (4, 17) and increased parasympathetic reflex airway activity (3). Our findings therefore might reflect that the patients in this study had asthma of only mild to moderate severity. Dose-response studies with ipratropium bromide have yielded conflicting results. However, in some patients with asthma an ipratropium bromide dose of up to at least 0.5–1 mg has been found to have an increasing bronchodilatory effect (9, 11, 25). Thus, one possible explanation for the low number of subjects in this study, to achieve substantial bronchodilating effect of ipratropium bromide may be that the dose was sub-optimal. However, it seems more likely that considerable bronchial response to inhaled ipratropium bromide occurs mainly in a particular subgroup of patients with asthma, as suggested by Brown et al. (5), and that our study included relatively few "responders". This remains hypothetical, however, since our data do not allow unequivocal identification of such "responders". If the 55 patients in this study, who were found to be nonresponders, had been tested with ipratropium bromide on a day when they had reduced lung function, they might have turned out to be responders. However, our findings indicate that the degree of involvement of parasympathetic pathways in bronchomotor responses, as expected, varies among children and adolescents with asthma, as it has been found in adults with bronchial asthma (8).

It has earlier been shown that the bronchodilator effect of ipratropium bromide peaks 1 h after inhalation and virtually disappears within 6 h (16); but the second part (the investigational trial) of this study showed that the maximum response to inhaled ipratropium bromide has already been reached 30 min after the inhalation. Thus, the reason why so many of the subjects in this study were found to have insignificant bronchial response to inhaled ipratropium bromide can not be that its bronchodilating effect had not yet reached maximum at the time when the lung function was measured.

This study showed that ipratropium bromide inhaled from a powder delivery system is at least as effective as inhalation from a dosi-aerosol. This might be of importance in the treatment of young children with bronchial asthma, because powder is easier to inhale than aerosol.

We conclude that our findings do not support the use of ipratropium bromide as an additional treatment for children and adolescents with asthma of mild to moderate severity, unless the subjects beforehand have been shown to be responders. We also conclude that the bronchodilating effect of ipratropium bromide is the same whether the drug is

administered as powder or as aerosol. We suggest that higher doses of ipratropium bromide than presently recommended should be tested in controlled trials in the treatment of chronic, stable asthma in children and adolescents.

References

1. BACH-MORTENSEN N. Experience with the inhalation of Berotec powder in the treatment of asthma in children. *Eur J Respir Dis* 1983; 64, Suppl. 130, 25-7.
2. BOUSHEY HA, HOLTZMAN MJ. Autonomic regulation of airways: Parasympathetic nervous system. In: WEIS EB, SEGAL MS, STEIN M (eds.): *Bronchial asthma: mechanisms and therapeutics*, 2nd ed. Little, Brown, 1984.
3. BOUSHEY HA, HOLTZMAN MJ, SHELLER JR, et al. State of the art: bronchial hyperreactivity. *Am Rev Respir Dis* 1980; 121: 389-413.
4. BROOKS SM, MCGOWAN K, BERNSTEIN L, et al. Relationship between number of beta adrenergic receptors in lymphocytes and disease severity in asthma. *J Allergy Clin Immunol* 1979; 63: 401-6.
5. BROWN IG, CHAN CS, KELLY CA, DENT AG, ZIMMERMAN PV. Assessment of the clinical usefulness of nebulised ipratropium bromide in patients with chronic airflow limitation. *Thorax* 1984; 39: 272-6.
6. DAHL R. Dosis-aerosolbehandling. Inhalationstekniske vanskeligheder for spraybehandlede. *Ugeskr Laeg* 1977; 139: 1856-7 (summary in English).
7. GROGGINS RC, MILNER AD, STOKES GM. Bronchodilator effects of clemastine, ipratropium bromide, and salbutamol in preschool children with asthma. *Arch Dis Child* 1981; 56: 342-4.
8. GROSS NJ. Sch 1000: A new anticholinergic bronchodilator. *Am Rev Respir Dis* 1975; 112: 823-5.
9. HARTLEY JPR, DAVIES BH. Cholinergic blockade in the prevention of exercise-induced asthma. *Thorax* 1980; 35: 680-5.
10. HODGES IGC, GROGGINS RC, MILNER AD, STOKES GM. Bronchodilator effect of inhaled ipratropium bromide in wheezy toddlers. *Arch Dis Child* 1981; 56: 729-32.
11. HOWARTH PH, STAINFORTH JN, HOLGATE ST. Bronchodilator efficacy of nebulised salbutamol and ipratropium bromide in chronic airflow obstruction. *Thorax* 1982; 37: 789-93.
12. KATZUNG BG (ed.) *Basic & clinical pharmacology*, 2nd ed. Lange Medical Publications, Los Altos, CA, 1984: 234-5.
13. LICHTERFELD A. Safety of Atrovent. *Scand J Respir Dis* 1979; 60: Suppl. 103, 143-4.
14. LIN MT, LEE-HONG C, COLLINS-WILLIAMS C. A clinical trial of the bronchodilator effect of SCH 1000 aerosol in asthmatic children. *Ann Allergy* 1978; 40: 326-8.
15. MANN NP, HILLER EJ. Ipratropium bromide in children with asthma. *Thorax* 1982; 37: 72-4.
16. PAKES GE, BROGDEN RN, HEEL RC, SPEIGHT TM, AVERY GS. Ipratropium bromide: a review of its pharmacological properties and therapeutic efficacy in asthma and chronic bronchitis. *Drugs* 1980; 20: 237-66.
17. PARKER CW, SMITH JW. Alterations in cyclic adenosine monophosphate metabolism in human bronchial asthma. I. Leucocyte responsiveness to β -adrenergic agents. *J Clin Invest* 1973; 52: 48-59.
18. PEDERSEN S, STEFFENSEN G. Fenoterol powder inhaler technique in children: influence of inspiratory flow rate and breathholding. *Eur J Respir Dis* 1986; 68: 207-14.
19. PEDERSEN S, ØSTERGAARD PAA. Nasal inhalation as a cause of inefficient pulmonary aerosol inhalation technique in children. *Allergy* 1983; 38: 191-4.
20. PETRIE GR, PALMER KNV. Comparison of aerosol ipratropium bromide and salbutamol on chronic bronchitis and asthma. *Br Med J* 1975; 1: 430-2.
21. RUFFIN RE, FITZGERALD JD, ROEBUCK AS. A comparison of the bronchodilator activity of Sch 1000 and salbutamol. *J Allergy Clin Immunol* 1977; 59: 136-41.
22. STOKES GM, MILNER AD, HODGES IGC, HENRY RL. Nebulized ipratropium bromide in wheezy infants and young children. *Eur J Respir Dis* 1983; 64: Suppl. 128, 494.
23. THIESSEN B, PEDERSEN OF. Maximal expiratory flows and forced vital capacity in normal, asthmatic and bronchitic subjects after salbutamol and ipratropium bromide. *Respiration* 1982; 43: 304-16.
24. WARD MJ, FENTEM PH, SMITH WHR, DAVIES D. Ipratropium bromide in acute asthma. *Br Med J* 1981; 282: 598-600.
25. WILSON N, DIXON C, SILVERMAN M. Bronchial responsiveness to hyperventilation in children with asthma: inhibition by ipratropium bromide. *Thorax* 1984; 39: 588-93.
26. ZAPLETAL A, SAMANEK M, PAUL T. Lung function in children and adolescents. Methods, reference values. In: HERZOG H. Karger, Switzerland, 1987: 1-220.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.