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The Protective Effects of Ipratropium Bromide and Terbutaline on Distilled Water-induced Bronchoconstriction

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SUMMARY: In a randomized, double-blind, placebo-controlled study, we investigated the protective effects of ipratropium bromide 160 μg and 320 μg and terbutaline 500 μg on ultrasonically nebulized distilled water (UNDW)-induced bronchoconstriction in nine stable asthmatic patients. Both drugs caused a significant increase ($P < 0.001$) in baseline FEV_1 with no significant differences between the drugs or both doses of ipratropium bromide. Pre-inhalation of ipratropium bromide 320 μg and terbutaline 500 μg inhibited UNDW-induced bronchoconstriction ($P < 0.01$), whereas ipratropium bromide 160 μg had no protective effect. The protective effects of ipratropium bromide showed a large interindividual variation. There was no correlation between the increase in baseline FEV_1 and PD_{20}UNDW, indicating that the protective effect on UNDW-induced bronchoconstriction is not dependent on the bronchodilation induced by terbutaline and ipratropium bromide. It also appears that the UNDW-induced bronchoconstriction is at least partly vagally mediated.

KEY WORDS: Distilled water, Asthma, Protection, Ipratropium bromide, Terbutaline.

INTRODUCTION

Bronchial hyperresponsiveness is a major characteristic feature of bronchial asthma.[1] Inhalation of ultrasonically nebulized distilled water (UNDW) can induce bronchoconstriction in asthmatic subjects and has been used for assessment of bronchial hyperresponsiveness.[2] The underlying mechanism of UNDW-induced bronchoconstriction has not yet been elucidated. Pre-inhalation of sodium cromoglycate[2] and nedocromil sodium[3] can inhibit UNDW-induced bronchoconstriction, suggesting that mast cell-derived mediators are probably involved. Furthermore, the cholinergic nervous system seems to be involved, since pre-inhalation of atropine can prevent UNDW-induced bronchoconstriction.[4] The protective effects of the non-selective muscarinic receptor antagonist ipratropium bromide on UNDW-induced bronchoconstriction have not been clearly established. Doses normally used in clinical practice, i.e. 40 μg and 80 μg, have been reported not to show any protective effect. On the contrary, β_2-agonists, like salbutamol[5] and fenoterol,[6] can totally block the UNDW-induced bronchoconstrictor response.

The aim of this study was to investigate the effect of higher doses of ipratropium bromide on UNDW-induced bronchoconstriction. We used two different doses of ipratropium bromide to assess whether its effect is dose-dependent and we compared the effects of ipratropium bromide with those of a placebo and the β_2-agonist terbutaline.

PATIENTS AND METHODS

Subjects

Nine stable asthmatic subjects participated in the study. Their characteristics are given in Table 1. All patients, except for patient no. 9, were non-allergic with respect to history and negative reactions to a panel of intracutaneous skin tests (velvet, rye, cultivated and timothy grass, alder, birch, hazel, horse, cat, dog, house dust mite, and alternaria, cladosporium and aspergillus mould) (Pharmacia AB, Uppsala, Sweden).

Inhalation of a β_2-agonist induced an increase in FEV_1 of more than 15% and all patients reacted to inhalation of UNDW before the start of the trial with at least a 20% decrease in FEV_1. The use of β_2-agonists and ipratropium bromide was stopped for a period of 8 h before each test, but inhaled corticosteroids were continued without changing the dose

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Table 1 Patient characteristics.

Patient	Sex	Age (years)	FEV_1 (% predicted)	PD_{20}hist (μmol)	PD_{20}UNDW (ml)	Medication
1	F	24	90.9	0.20	6.5	a, b
2	F	33	118.3	0.18	1.4	a, b
3	M	53	56.8	0.03	1.3	a, b
4	M	50	61.4	ND	2.0	a, b
5	F	22	73.9	0.01	5.3	a
6	F	44	84.3	0.23	8.1	a
7	M	37	54.1	0.002	1.3	a, b, c
8	F	43	108.9	0.23	4.0	a, b
9	M	16	92.5	0.05	3.0	a, b
Mean		38.9	82.3	0.12	3.6	
SEM		4.3	7.6	0.04	0.8	

a: salbutamol; b: beclomethasone; c: ipratropium bromide.
ND: not done.

during the study. None of the patients had used systemic corticosteroids for a period of at least 3 months or suffered from a respiratory tract infection for a period of at least 1 month before the start of the study. The study was approved by the local Ethics Committee and all patients gave their written informed consent.

Study design

The patients attended the lung function laboratory on four different days at the same time of the day with intervals of at least one day. The baseline FEV_1 on those days had to be within 10% variation. After recording baseline flow-volume curves (Pneumoscreen II, Jaeger, Würzburg, Germany) the subjects inhaled the study medication. Ipratropium bromide was inhaled by means of a metered dose inhaler, 20 μg per puff, through a 750 ml spacer device, and terbutaline was inhaled as a powder by means of a turbuhaler(R) (Astra, Lund, Sweden), 500 μg per inhalation. In a double-blind and randomized order the patients inhaled the study medication. The study medication consisted of placebo (i.e. 4 times 4 puffs of placebo aerosol and 1 inhalation of placebo turbuhaler), ipratropium bromide 160 μg (i.e. 2 times 4 puffs of ipratropium bromide, 2 times 4 puffs of placebo aerosol and 1 inhalation of placebo turbuhaler), ipratropium bromide 320 μg (i.e. 4 times 4 puffs of ipratropium bromide and 1 inhalation of placebo turbuhaler) or terbutaline 500 μg (i.e. 1 inhalation of terbutaline turbuhaler and 4 times 4 puffs of placebo aerosol). Thirty minutes after inhalation of the test drugs an UNDW provocation test was performed.

Measurements

UNDW provocation tests were performed with the Ultraneb 99 ultrasonic nebulizer (DeVilbiss, Somerset, USA). The output was fixed at 2 ml/min without the equipment attached. The patients inhaled air with UNDW at tidal breathing through a mouthpiece with tightened lips and nose clipped. A Leardal IV two-way valve (Stavanger, Norway), with a dead space of 24 ml, was placed between the aerosol hose and the mouthpiece. A respirometer (British Oxygen Company, London, UK) was connected to the expiratory port of the two-way valve to measure the total volume of inhaled air. After inhalation of 20 l of ambient air through the system, doubling volumes of air with UNDW (3, 5, 10, 20, 40, 80, 160 l) were inhaled at 5-min intervals. Before and after the test the nebulizer chamber and aerosol hose were weighed and the total amount of inhaled distilled water was measured.

To assess bronchoconstriction, maximal expiratory flow-volume curves were recorded 30, 90 and 180 s after inhalation (Pneumoscreen II, Jaeger, Würzburg, Germany). The test was stopped when a 20% fall in FEV_1 had been achieved or the last dose of air with UNDW, i.e. 160 l, had been inhaled.

A dose–response curve was constructed on a semi-logarithmic scale. The PD_{20}UNDW, the cumulative dose of UNDW causing a 20% fall in FEV_1 from post-air values, was calculated by linear interpolation and expressed in ml H_2O.[9] If a 20% fall in FEV_1 was not achieved, the PD_{20}UNDW was equated to the total amount of inhaled UNDW.

Statistical analysis

The FEV_1 is expressed as a percentage of the predicted value.[10] The increase in FEV_1, 30 min after inhalation of the drugs, is expressed as a percentage of the baseline FEV_1. The changes in PD_{20}UNDW are expressed in doubling doses calculated from placebo values. All data were analysed by the Wilcoxon test and multiple comparison was performed with the Bonferroni correction. Correlations were calculated by the Spearman-rank test. All data are presented as means ± SEM. Statistical significance was accepted for $P < 0.05$.

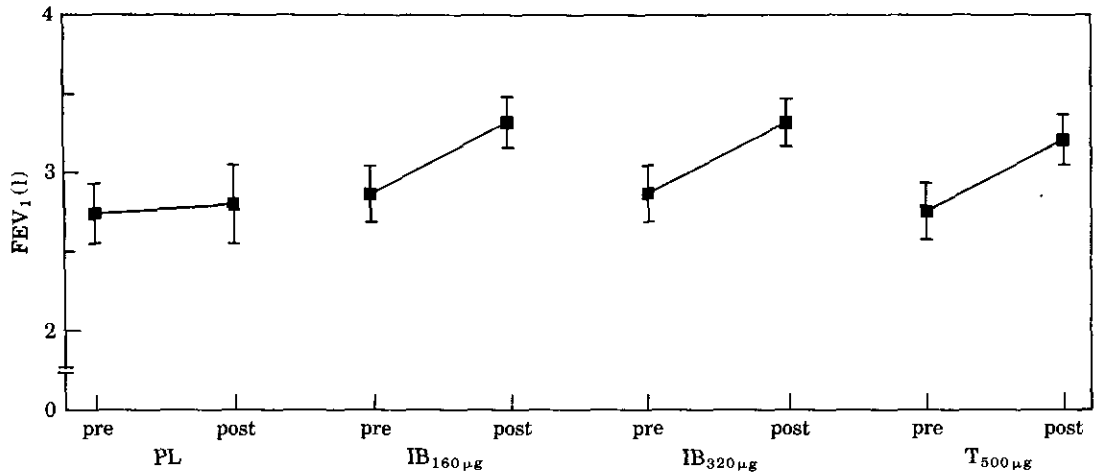

Fig. 1 The mean FEV_1 values (±SEM) before (pre) and 30 min after inhalation (post) of placebo (PL), ipratropium bromide 160 μg ($IB_{160\,\mu g}$) and 320 μg ($IB_{320\,\mu g}$), and terbutaline 500 μg ($T_{500\,\mu g}$), in nine asthmatic subjects.

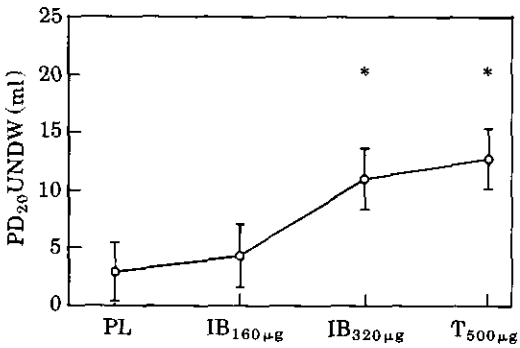

Fig. 2 Geometric means (±95% confidence interval) of the $PD_{20}UNDW$ after preinhalation of placebo (PL), ipratropium bromide 160 μg ($IB_{160\,\mu g}$) and 320 μg ($IB_{320\,\mu g}$), and terbutaline 500 μg ($T_{500\,\mu g}$), in nine asthmatic subjects (* $P<0.05$ vs. $IB_{160\,\mu g}$ and PL).

RESULTS

The baseline FEV_1 values on the four study days were not significantly different ($P=0.6$). The mean FEV_1 30 min after inhalation of the study drugs increased, as percentage of the baseline values, 1.0±2.7% after placebo ($P=0.45$), 17.7±3.1% after ipratropium bromide 160 μg ($P=0.008$), 17.5±3.3% after ipratropium bromide 320 μg ($P=0.008$) and 18.3±3.1% after terbutaline ($P=0.008$). The two doses of ipratropium bromide as well as terbutaline induced a similar increase in baseline FEV_1 (Fig. 1). The mean changes in $PD_{20}UNDW$ are shown in Figure 2. Ipratropium bromide 160 μg improved the $PD_{20}UNDW$ 0.6±0.3 doubling dose, which was not significantly different from the placebo ($P=0.17$). Ipratropium bromide 320 μg and terbutaline provided a significant protection against UNDW-induced bronchoconstriction compared to placebo and increased the $PD_{20}UNDW$ 1.9±0.4 and 2.1±0.4 doubling doses respectively ($P=0.002$). This protection was significantly better than that of ipratropium bromide 160 μg ($P=0.01$), but there was no significant difference in protection between ipratropium bromide 320 μg and terbutaline 500 μg ($P=0.38$). No significant correlation was found between the increases in FEV_1 30 min after inhalation and the changes in $PD_{20}UNDW$ induced by the drugs studied.

DISCUSSION

Protective effects of ipratropium bromide in asthmatic subjects have been demonstrated to pharmacological stimuli like histamine[11,12] and methacholine.[12,13] The doses of inhaled ipratropium bromide causing protection in these studies[11–13] varied from 40–80 μg. Eighty micrograms of ipratropium bromide showed significant protection in exercise-induced bronchoconstriction,[12] although there was a very large variation of the individual responses. In eucapnic voluntary hyperventilation- and distilled water-induced bronchoconstriction, preinhalation of 80 μg of ipratropium bromide had no protective effects, whereas β_2-agonists provided significant protection.[5,14] Inhaled β_2-agonists have been shown to inhibit histamine and methacholine-induced bronchoconstriction in therapeutic doses of 200 μg.[15,16]

In this study we have demonstrated that preinhalation of ipratropium bromide 320 μg or terbutaline 500 μg can diminish the UNDW-induced bronchoconstrictor response in asthmatic patients. Preinhalation of ipratropium bromide 160 μg increased the baseline FEV_1 significantly and to the same degree as ipratropium bromide 320 μg and terbutaline 500 μg. However, ipratropium bromide 160 μg did not inhibit UNDW-induced bronchoconstriction significantly,

although in two patients (nos. 8 and 9) the shift in PD_{20}UNDW was more than 2 doubling doses.

We did not find a correlation between the increase in FEV_1 and the degree of protection, which indicates that the protective effect was not solely due to the bronchodilator response of the drugs. This observation suggests that the protective effect of ipratropium bromide is related to the amount of inhaled drug. These findings are supported by the results of other studies.[5,17] Doses of 80 μg inhaled ipratropium bromide had no protective effect, whereas doses above 200 μg induced a significant protection against UNDW-induced bronchoconstriction. The mechanism of the inhibition by ipratropium bromide of the UNDW-induced bronchoconstriction in asthmatics is not known. In contrast to β_2-agonists, ipratropium bromide has no stabilizing effects on mast cell degranulation as shown during allergen provocation.[18] Decreased airway smooth muscle supersensitivity,[19] or an ipratropium bromide-induced inhibition of a vagal reflex,[20] might be the mode of action of this drug. Since the protective effect of muscarinic receptor antagonists to bronchoconstrictor stimuli only appears to be mediated through the inhibition of acetylcholine release,[21] our results support the idea that bronchoconstriction induced by UNDW in asthmatics is at least partially mediated by a vagal reflex mechanism. Why a dose of 160 μg ipratropium bromide provides maximal bronchodilation, whereas a dose of 320 μg is required to protect against UNDW-induced bronchoconstriction, is not clear. Ipratropium bromide is a non-selective muscarinic receptor antagonist and therefore differences in inhibition of pre- and postjunctional muscarinic receptors are difficult to interpret.

Our data show a large individual variation in the protective effect of ipratropium bromide 320 μg on UNDW-induced bronchoconstriction. This finding is confirmed by Ihre and Larsson,[22] who found a remarkable interindividual variation in bronchodilation and protection for histamine-induced bronchoconstriction due to ipratropium bromide, whereas they found only a small intraindividual variation. Probably the interindividual variation in our results might also contribute to the different effects of the two doses of ipratropium bromide.

The protective effect of terbutaline was not complete in all subjects. This was not what we had expected, since β_2-agonists like salbutamol have been reported to totally block UNDW-induced bronchoconstriction.[5] Terbutaline 500 μg, however, showed significantly less protection in histamine-induced bronchoconstriction than fenoterol 400 μg and salbutamol 200 μg,[15] which may support our findings.

We conclude that in comparison with a standard dose of terbutaline only high-dose inhaled ipratropium bromide provides significant protection against UNDW-induced bronchoconstriction, although there is a large interindividual variation in the protective effect. This inhibition is not solely related to the bronchodilator effect of ipratropium, but is probably also due to the blockade of a vagally-mediated reflex induced by UNDW.

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