A Comparative Study of Various Combinations of Ipratropium Bromide and Metaproterenol in Allergic Asthmatic Patients*

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The bronchodilator effect of ipratropium bromide (IB) (Atrovent-Sch 1000), 40 μg inhaled, and metaproterenol (Met), 1.25 mg in various combinations, was compared in ten allergic asthmatic patients, aged 23 to 63 years. Six combinations were used at random in a double blind study. The following ventilatory functions—FVC, TGV, SGaw, FEV1, FEF 25-75, \( V_{250} \), \( V_{250} \), were measured at 30 min. intervals for the first two hours and at 60 minute intervals for the additional three hours. Inhalation of IB followed by Met resulted in additive bronchodilator effect that was significantly greater and longer than IB alone (p<0.05), Met alone (p<0.05), two consecutive inhalations of Met (p<0.05), or Met followed by IB (p<0.05). The bronchodilating effect of IB and Met after five hours was the same as IB after one hour.

The bronchodilator effect of N-isopropyl acid ester of atropine (ipratropium bromide [IB], Sch 1000—Atrovent) in asthmatic and bronchitic patients is well reviewed.1,2 Since the mechanism of action of anticholinergic drugs is different from beta-adrenergic agonist drugs, the combination of IB with beta-adrenergic agonists might result in a synergistic bronchodilating effect. Reports of such synergism have been published, although statistical significance was not invariably present.3,4

In the present study, we compared six possible therapeutic combinations of IB, metaproterenol (Met), and placebo, in a group of allergic asthmatic patients, for synergistic antagonistic or additive effects.

**Material and Methods**

The allergic asthmatic group consisted of 16 patients (seven women and nine men) aged 23 to 63 years, with clinical diagnosis of moderate to severe asthma, based upon history, physical examination, positive skin tests, and lung function tests. Patients with an increase of more than 20 percent in FEV1 and FEF25-75 after inhaling 400 μg of albuterol were included in the study.

Six combinations of IB and Met were given at random and in a double-blind fashion as follows: IB and placebo; IB and IB; IB and Met; Met and placebo; Met and Met; and Met and IB. The drugs were administered with a metered dose inhaler (MDI), and the second drug of each combination was given one hour after the first one. The dose of IB was 40 μg, and the dose of Met was 1.25 mg. The following ventilatory tests were performed: FVC; FEV1; FEF25-75; \( V_{250} \); \( V_{250} \); TGV, and SGaw. These were done at 30 minute intervals for the first two hours and at 60 minute intervals for the additional three hours. The best of three measurements was taken. Patients in whom on any study day the baseline of FEV1 changed by more than 15 percent from the control value on the first day were excluded from the study (six out of 16 patients were excluded for this reason). Patients receiving corticosteroid therapy equivalent to, or less than, 10 mg of prednisone per day, were included. The steroids, bronchodilators, and antihistamines were withheld for at least 12 hours prior to testing. Patients with heart diseases, renal or metabolic disease, glaucoma, sensitivity to atropine, or pregnant women were not included in the study. All patients gave written consent for the study.

**Statistical Analysis**

Each patient was observed repeatedly at several time points. These measurements are correlated. The statistical analysis aimed at comparing the efficiency of the six combinations of treatments has to account for this lack of independence. For each ventilatory function, an analysis of variants was performed with repeated measurements as implemented in the computer program BM2P2V.5,6 This method of analysis allows for two basic tests: (1) whether the mean responses in the tested treatments are the same (where the mean is defined over all the time points); and (2) whether the shapes of the response curves over time change from one treatment to another (interaction between treatment and times).

**Results**

Figure 1 summarizes the changes in FEV1 in ten allergic asthmatic patients when the first inhalation was IB and the second inhalation was Met, IB or placebo. The IB alone resulted in a maximal increase in FEV1 (22 percent) after 90 minutes. Inhalation of IB followed by second inhalation of IB resulted in a better
and prolonged bronchodilator effect than IB alone. The most effective bronchodilatation was achieved with the combination of IB followed by Met. The peak effect (48 percent increase in FEV₁) occurred two hours after the inhalation of IB and one hour after Met. Five hours after the first inhalation, the increase in FEV₁ was still 25 percent, i.e., similar to the peak effect of IB alone. When the two drugs were given in a reversed sequence (Fig 2), significant differences were noted between the various combinations of Met with IB, placebo, or Met in the same patient. Curve comparisons of the efficiency of various paired treatments showed that the bronchodilator effect of IB with Met was statistically significant for all the factors measured (FEV₁, FEF₂₅₋₇₅%, SGAW) as compared to IB alone (p < 0.05), Met alone (p < 0.05), consecutive inhalations of IB or Met (p < 0.05), or Met followed by IB (p < 0.05).

The bronchodilator effect of IB and Met proved to be additive and was maintained throughout the five hours. The combined effect of 48 percent increase in FEV₁ (Fig 3) after two hours is the sum total of the two drugs (IB had 20 percent increase after two hours and Met a 30 percent increase after one hour). The same results are seen also three, four, and five hours after the first inhalation for all the ventilatory functions measured.

**DISCUSSION**

In a number of studies, the combined use of IB with beta₂ adrenoceptor agonist drugs produced a greater or more prolonged response than occurred with the individual drugs. However, in most studies, the small number of patients and the heterogeneity of the groups made statistical analysis inconclusive.

From our results it is evident that the best combination in allergic asthmatic patients was inhalation of IB followed by Met. The bronchodilator effect achieved by this combination proved to be additive throughout the five hours. By reversing the order of the drugs, this additive effect was not obtained. Similar results were reported by Douglas et al. for IB and albuterol in chronic bronchitis patients.

The reason for the additive effect of the two drugs is not known. Some possible explanations for the sequencing effect include the following:

(a) The IB has a greater bronchodilator effect on the central airways than adrenergic stimulator drugs and hence may cause a more favorable deposition of Met when this is given as a second inhalation.

(b) In asthmatic and bronchitic patients in whom
increased vagal tone is usually present, the additive effect with beta₂ adrenoceptor agonists may conceivably be achieved only in the presence of decreased vagal tone.

(c) It is known that the peak effect of IB occurs later than that of beta agonist drugs. 17,18

In our patients, maximal bronchodilation occurred 30 minutes (Fig 2) after Met inhalation when given alone and 90 minutes (Fig 1) after IB inhalation when given alone. This time difference of peak effect of the two drugs can possibly explain the additive as well as the lack of additive effect when the two drugs are given in a reverse order. When Met follows IB, the IB has not yet reached its peak effect, thus enabling an additive effect to occur. When IB follows Met, the latter reaches its peak after 30 minutes, well before IB is given, and thus preventing further bronchodilatation.

In conclusion, ipratropium bromide may prove a useful adjuvant to therapy with beta₂ stimulants in multiple drug regimens and may also reduce the usual dose of sympathomimetic drugs in patients in whom side effects are troublesome. 19,20

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