

Comparison of Inhaled Terbutaline and Inhaled Terbutaline Plus Ipratropium Bromide in Acute Asthmatic Children

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The use of aerosols in the treatment of acute asthmatic attack is rapidly becoming the preferred form of bronchodilator therapy.¹⁻³ Terbutaline, a selective beta-2-adrenergic agonist, used as an aerosol provides rapid bronchodilatation with less systemic side effects in comparison with oral or parenteral therapy.⁴⁻⁷ The use of this drug in a pressurized inhaler with the attachment of a 750 ml spacer has been shown to increase the availability of the drug to the patient,⁸ and the deposition of the drug in the lungs.⁹ Patients can inhale an adequate number of puffs without stress and need no coordination of operation and inhalation. It is clinically as effective as a fourfold dose via a nebulizer.¹⁰ Ipratropium bromide, a quaternary ammonium compound, has been found to have similar bronchodilator activity as other anticholinergic agents but with less frequent side effects.¹¹⁻¹² This drug, although able to dilate narrow airways, is not usually as effective as sympathomimetic drugs in treating asthma.¹³⁻¹⁸ However, additive effects of this drug to that of the sympathomimetics have been shown in some studies,^{15,19,20} but not in others.^{14,18} Only a few studies^{21,22}

SUMMARY Twenty asthmatic children, aged 4 to 15 years, consisting of 14 boys and 6 girls, were studied during acute episodes of asthmatic attacks. A group of 10 children each received either inhaled terbutaline 0.5 mg or inhaled terbutaline 0.5 mg followed by ipratropium bromide 0.04 mg 15 minutes later through a 750-ml volumetric spacer. Significant increases in FEV₁ over the baseline were observed from 2 minutes to 2 hours and from 2 minutes to 6 hours following the first and second regimen respectively. A slightly greater increase and longer duration in FEV₁ were observed in the combined drug treatment and very slight decreases in systolic and diastolic blood pressure below the base-line were observed. Neither regimen showed any serious adverse effect on the heart rate and respiratory rate.

of the two drugs given in sequence have been done, both in adults. It was the objective of this study to compare the bronchodilating and cardiovascular effects of inhaled terbutaline when given alone and when given in the sequence of inhaled terbutaline followed by inhaled ipratropium bromide 15 minutes later. Either regimen using the metered dose inhaler was delivered with a 750 ml spacer interposed between the actuator and the mouth.

MATERIALS AND METHODS

Patients

Twenty asthmatic children, 4 to 15 years of age consisting of 14 boys and 6 girls, were studied while having acute asthmatic attacks which had occurred as acute onset few

hours prior to the study. All had histories of recurrent, reversible, generalized wheezing, for which they were receiving treatment at the pediatric allergy clinic of Ramathibodi Hospital, Bangkok, Thailand. The details of the patients studied are shown in Table 1.

Methods

Each child received either 0.5 mg (2 puffs) of inhaled terbutaline or inhaled terbutaline 0.5 mg plus

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inhaled ipratropium bromide 0.04 mg (2 puffs) 15 minutes later. These were given as pressurized aerosols inhaled through a 750 ml volumetric spacer. Two groups consisting of 10 children each were selected randomly. Forced expiratory volume in one second (FEV₁), blood pressure, heart rate and respiratory rate were obtained in that order before treatment and 2,5,15,30,60,120,180,240 and 360 minutes after treatments. All FEV₁ were measured with the same electronic spirometer (Microspiro HI-298, Chest Corporation, Japan) while the patients were seated and the best value of three measurements for each time period was used. Parents were informed of the procedures and consents were obtained.

Statistical analysis

Paired and unpaired *t*-test were used to analyze the data.

RESULTS

For each protocol, all measurement variables were expressed as a percentage of the base-line, pre-aerosol value. The mean percent changes in FEV₁ after inhaled terbutaline and inhaled terbutaline plus inhaled ipratropium bromide in sequence are shown in Fig. 1. Rapid onset of bronchodilatation following either regimen was observed within 2 minutes with a significant increase in FEV₁ from the base-line ($P < 0.05$). The maximum FEV₁ was observed at 30 minutes in both regimens and a significant increase was observed in FEV₁ lasting for 2 hours following inhaled terbutaline alone ($P < 0.05$) and for 4 hours following inhaled terbutaline plus inhaled ipratropium bromide ($P < 0.05$). The overall FEV₁ following the second regimen was higher than that following the first one throughout the 6 hour study period, but the difference did not reach statistical significance.

The mean percent changes in heart rate, blood pressure and respiratory rate are shown in Fig. 2, 3

Table 1. Details of the patients studied

	Inhaled terbutaline	Inhaled terbutaline plus inhaled ipratropium bromide	Total
No. of patients	10	10	20
Age (yr) : range	4 - 12	5 - 14.6	4 - 14.6
mean \pm SD	9.2 \pm 2.9	8.3 \pm 2.8	8.8 \pm 2.8
Sex : boys	7	7	14
girls	3	3	6
Weight (kg) : range	14.0 - 42.0	16.0 - 53.5	14 - 53.5
mean \pm SD	27.8 \pm 9.7	24.8 \pm 10.9	26.2 \pm 10.2
Height (cm) : range	99 - 142	103 - 154	99 - 154
mean \pm SD	129 \pm 14	122.7 \pm 15.7	125.7 \pm 14.8
Duration of asthma (yr) :			
range	1.5 - 11.4	0.4 - 6.7	0.7 - 11.4
mean \pm SD	6.2 \pm 3.3	3.6 \pm 1.9	4.9 \pm 2.9

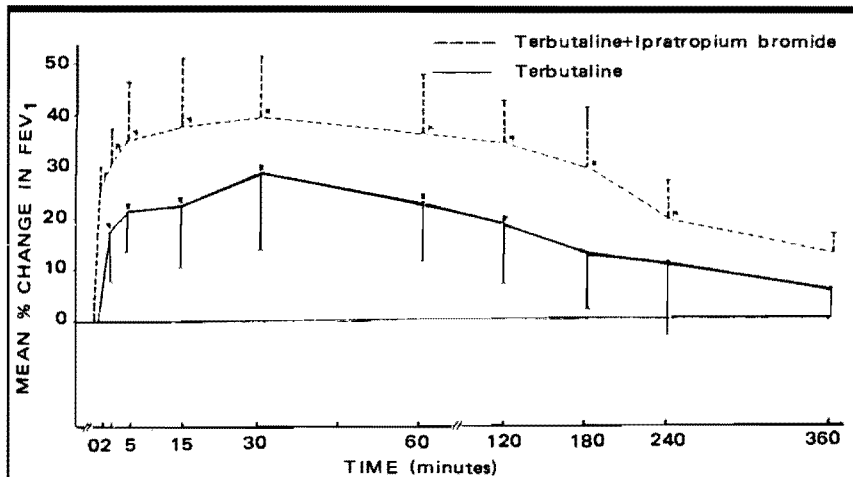


Fig. 1 Mean percent change in FEV₁ after inhaled terbutaline 2 puffs (0.50 mg) only and inhaled terbutaline (2 puffs) followed by ipratropium bromide 2 puffs (0.04 mg) 15 minutes later. Each point represents mean \pm SE. The asterisks indicate statistical significance from the baseline ($p < 0.05$).

and 4. A small but significant increase in heart rate was observed at 5 minutes following inhaled terbutaline alone and a significant increase was observed at 2 and 5 minutes following inhaled terbutaline plus inhaled ipratropium bromide ($P < 0.05$) but there were no significantly statistical differences between the two regimens.

Slightly insignificant increases were observed in both systolic and

diastolic blood pressure above the baseline following inhaled terbutaline and decreases below the baseline were observed following the inhaled terbutaline plus inhaled ipratropium bromide. Small increases in respiratory rate was observed in both regimens.

DISCUSSION

The results of this study show

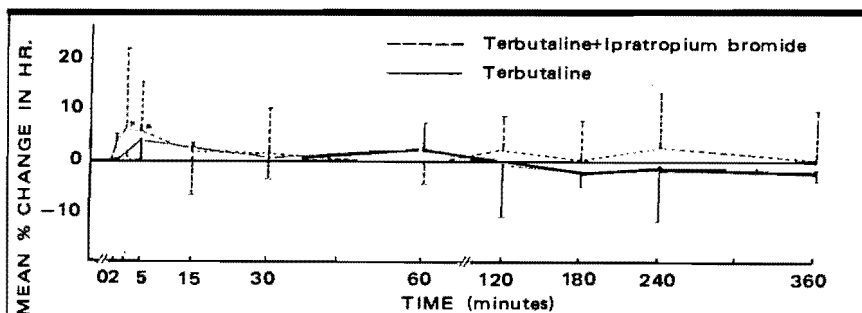


Fig. 2 Mean percent change in HR after inhaled terbutaline 2 puffs (0.05 mg) only and inhaled terbutaline (2 puffs) followed by ipratropium bromide 2 puffs (0.04 mg) 15 minutes later. Each point represent Mean \pm SE. The asterisks indicate statistical significance from the baseline ($p < 0.05$)

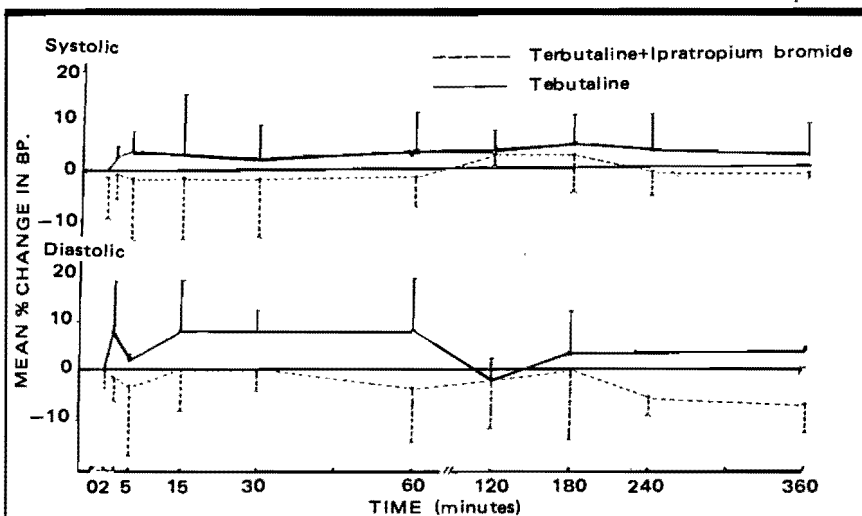


Fig. 3 Mean percent change in BP after inhaled terbutaline 2 puffs (0.50 mg) only and inhaled terbutaline (2 puffs) followed by ipratropium bromide 2 puffs (0.04 mg) 15 minutes later. Each point represents mean \pm SE.

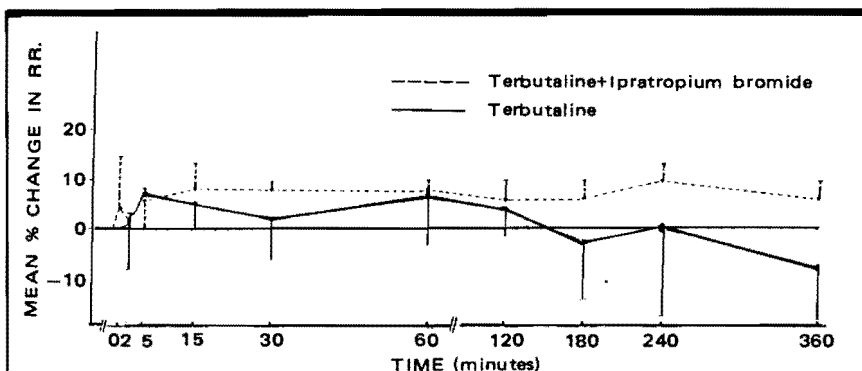


Fig. 4 Mean percent change in RR after inhaled terbutaline 2 puffs (0.50mg) only and inhaled terbutaline (2 puffs) followed by ipratropium bromide 2 puffs (0.04 mg) 15 minutes later. Each point represents mean \pm SE.

that the combination of the two drugs, inhaled terbutaline followed by inhaled ipratropium bromide 15 minutes later produced a slightly greater and longer response in FEV_1 throughout the 6 hours study period in comparison with inhaled terbutaline alone and also slight decreases in systolic and diastolic blood pressure below the baseline. There were no serious cardiovascular side effects. This is in agreement with some previous studies^{21,22} using the combination of sympathomimetic and cholinergic drugs but not in others.^{18,20}

Ipratropium bromide act through receptor and biochemical pathways different from those of sympathomimetics. Previous reports^{13,15} have in general suggested that anticholinergic agents are less effective bronchodilators than beta-2-adrenergic receptor agonists in patients with asthma and it should not be used as a single drug therapy in acute asthmatic exacerbation. Combination therapy with sympathomimetic and anticholinergic nebulizer solutions was found to be more efficacious than either agent alone.^{15,19,20,23} Ward *et al*²² looked at the sequential effects of ipratropium bromide and salbutamol in adults using nebulized salbutamol followed by ipratropium bromide 2 hours later: the two drug regimen produced greater bronchodilatation than either used alone. Sergysels *et al*²¹ suggested that the combination of a sympathomimetic followed by ipratropium bromide one hour later showed a more prolonged period of bronchodilatation than either drug alone.

Possible cardiovascular, ocular, secretion-drying and facial-flushing effects of atropine like drugs were not encountered in our study. Furthermore, the systolic and diastolic blood pressures in the combination drug treatment were lower in comparison with the single terbutaline treatment. This may be of advantage.

In conclusion, this study showed that the combination drug regimen of inhaled terbutaline followed by inhaled ipratropium bromide 15 minutes later had greater bronchodilatation throughout the 6-hour study period in acute asthmatic children in comparison with inhaled terbutaline alone but the difference did not reach statistical significance. There were no adverse effects on blood pressure, heart rate and respiration rate. In acute exacerbations, ipratropium bromide given in sequence following terbutaline may be a useful adjunctive agent in the treatment of asthma.

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