

ORIGINAL ARTICLES

A Comparison of Different Intervals of Administration of Inhaled Terbutaline in Children with Acute Asthma

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Bronchial asthma is a common disease and a frequent cause of emergency room and physician's office visits. Many different types of drugs have been found to be safe and effective in treating acute episodes.¹⁻⁴ Among these drugs, the β_2 -adrenergic agonists are undoubtedly very effective bronchodilators.⁵⁻⁸ Terbutaline is a selective β_2 -adrenergic bronchodilator having a rapid onset of action, long duration and less cardiovascular side effects.⁹⁻¹² Inhalation of this drug has been shown to give bronchodilatation as effectively as the parenteral administration¹³⁻¹⁷ and more effectively than the oral route¹⁵ with less systemic side effects.

Inhaled terbutaline from a metered aerosol with the use of spacer or large volume spacer of 750 ml showed an increase in the availability of the drug to the patient resulting in higher bronchodilatation¹⁷⁻²¹ than with the conventional one. A dose-dependent increase in FEV₁ or PEF of terbutaline in previous studies^{13,18,22,23} has been observed but relatively little work has been done on the frequency of administration, in adults^{18,23,24} and children.²⁵ It was the objective of this study to compare the bronchodila-

SUMMARY Thirty asthmatic children, 5 to 14 years of age, 20 boys and 10 girls, were studied while having acute asthmatic attacks. Each group of 10 children received either a single dose of 6 puffs (1500 μ g) or 3 doses of 2 puffs (500 μ g) at 5-minute or 15-minute intervals of terbutaline pressurized aerosol inhaler through a 750-ml volumetric spacer. The onset of bronchodilatation was observed within 2 minutes in all. The 3 doses at 15-minute intervals gave the greatest bronchodilatation throughout the 6-hour study period in comparing with the other two regimens. Slightly insignificant increases in systolic blood pressure and heart rate were observed in all groups and there were no statistically significant differences among them. No serious side effects were observed.

tation and cardiovascular side effects of inhaled terbutaline with use of a spacer between total single dose and three divided doses at 5-minute and 15-minute intervals.

PATIENTS AND METHODS

Patients

Thirty asthmatic children aged 5 to 14 years, twenty boys and ten girls, were studied while having acute asthmatic attacks which had acute onset a few hours prior to the study. All had histories of recurrent, reversible, generalized airway obstruction, for which they were receiving treatment through the pediatric allergy clinic at Ramathibodi Hospital, Bangkok, Thailand. Details of patients are shown in Table 1.

Methods

Children were randomized to receive inhaled terbutaline via a 750-ml volumetric spacer (Nebuhaler, Draco AB, Lund, Sweden) either a single dose of 6 puffs (1500 μ g) or 3 divided doses of 2 puffs (500 μ g) each at 5-minute or at 15-minute intervals. Data of forced expiratory volume in one second (FEV₁), blood

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Table 1. Demographic data of the patients

	Terbutaline inhalation			Total
	Single dose (1500 μ g)	Three doses at 5 min. intervals (500 μ g x 3)	Three doses at 15 min. intervals (500 μ g x 3)	
No. of patients	10	10	10	30
Age (yr)	5-14	5-13	5-13	5-14
mean \pm SD	9.4 \pm 2.9	9.2 \pm 3.3	9.2 \pm 2.6	9.2 \pm 2.8
Sex : Boys	7	5	8	20
Girls	3	5	2	10
Weight (kg)	16-42	14-41	14-40	14-42
mean \pm SD	28.4 \pm 11.4	26.2 \pm 8.3	26.2 \pm 8.4	26.9 \pm 9.1
Height (cm)	110-165	118-150	101-149	101-165
mean \pm SD	129.9 \pm 16.9	127 \pm 14.8	128.3 \pm 13.8	128.4 \pm 14.8
Duration (yr)	0.02-10	0.8-11	0.2-11	0.02-11
mean \pm SD	4.4 \pm 3.4	6.5 \pm 3.8	4.8 \pm 3.6	5.2 \pm 3.7

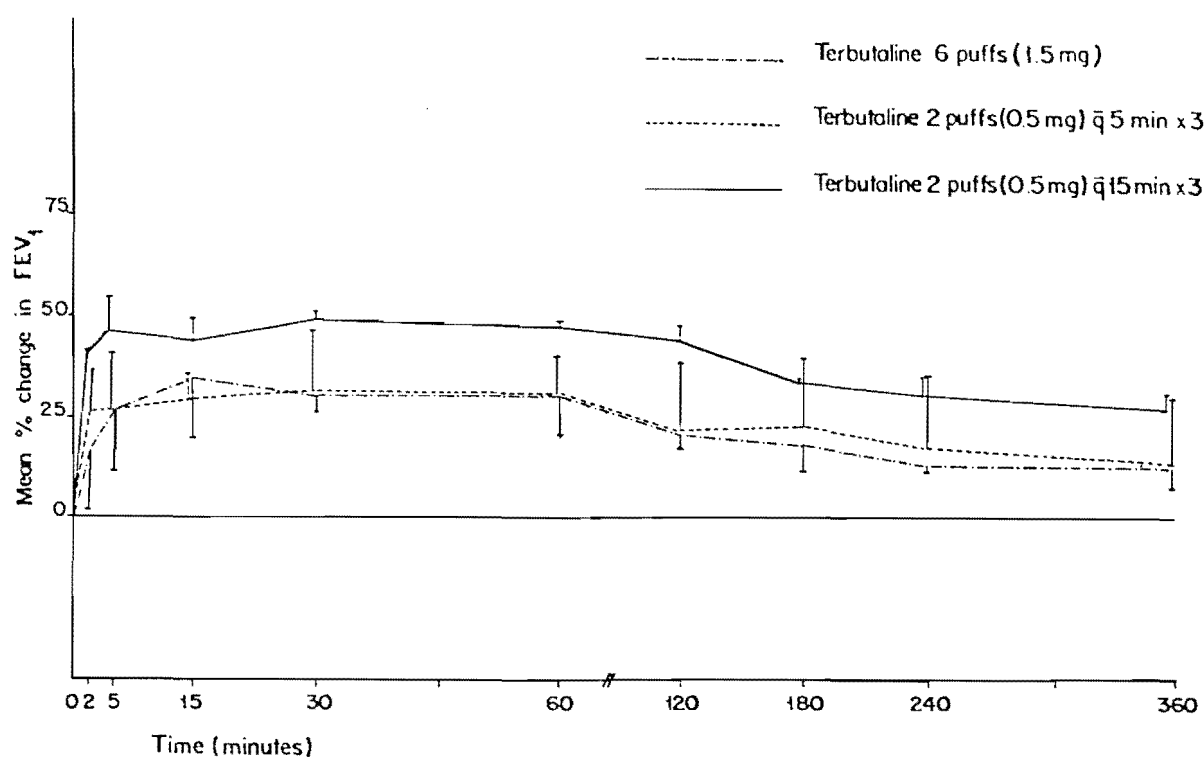
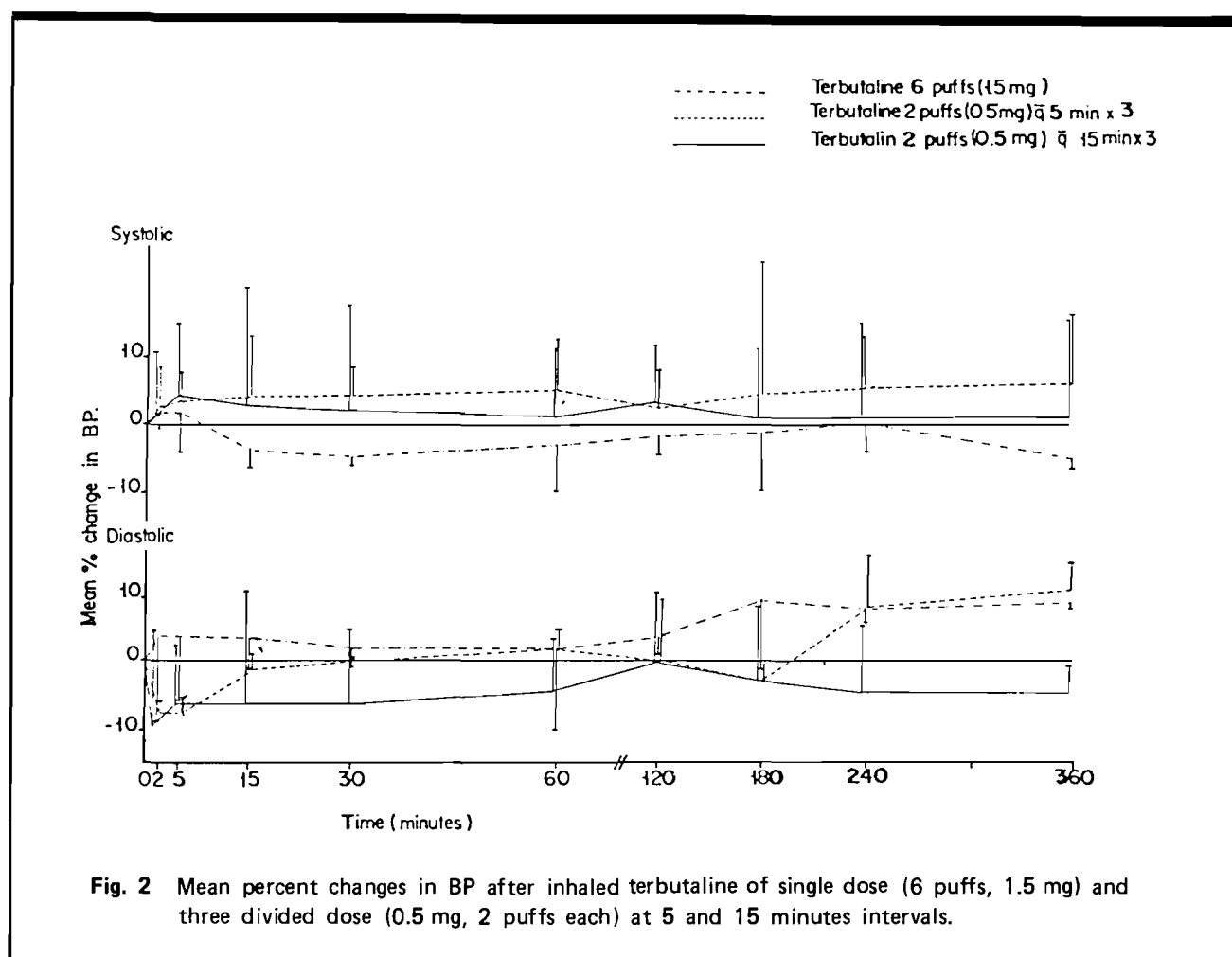


Fig. 1 Mean percent changes in FEV₁ after inhaled terbutaline of single dose (6 puffs, 1.5 mg) and tree divided dose (0.5 mg, 2 puffs each) at 5 and 15 minutes intervals.



pressure, heart rate, respiratory rate and any side effects were obtained before and 2, 5, 15, 30, 60, 120, 180, 240 and 360 minutes after each drug treatment. So the measurements at 2 minutes in the first, second and third group were 2, 12 and 32 minutes after the initial treatments, respectively. FEV₁ measurements using an electric spirometer (Microspiro HI-298, Chest corporation) were performed while the subjects were seated and the best value of three measurements was used. Parents were informed of the trial and written consents were given.

Statistical analysis

Kruskal-Wallis ANOVA, Mann-Whitney U-Wilcoxon rank sum W test and Wilcoxon matched-pairs

signed ranks test were used for the statistical analysis of the data.

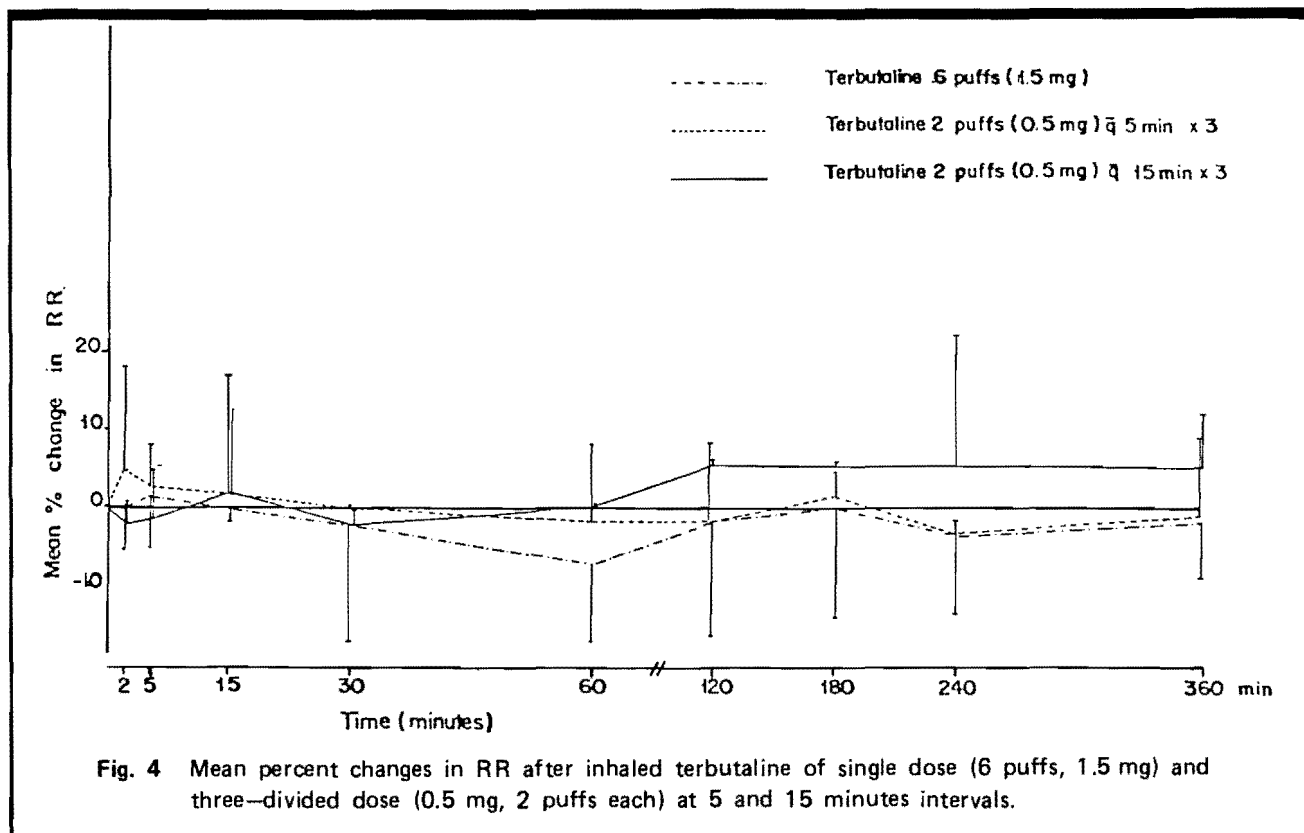
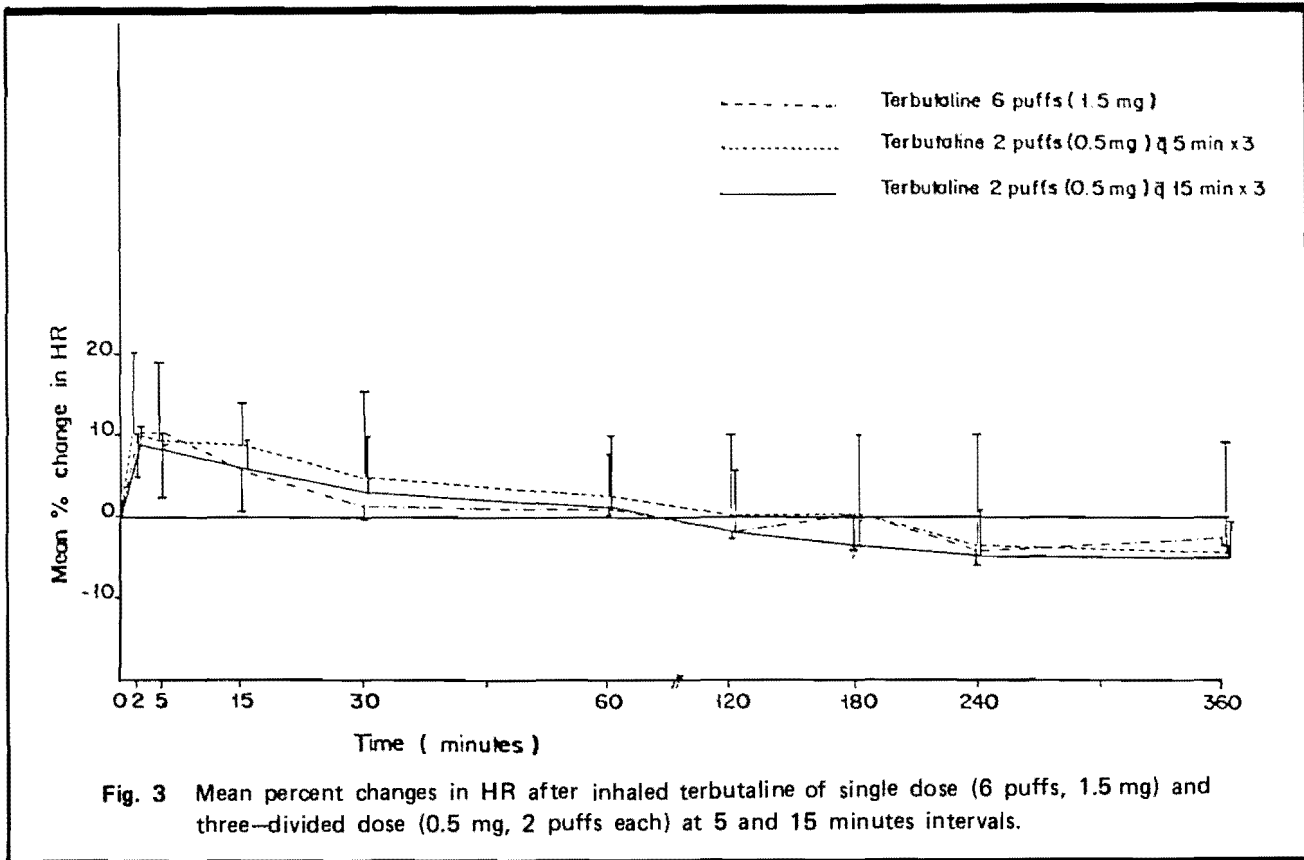
RESULTS

The mean percent changes in FEV₁ after the total single dose and the divided three-dose terbutaline inhalation at 5-minute intervals and 15-minute intervals are shown in Fig. 1. Rapid onset of bronchodilatation with significant increase in FEV₁ at 2 minutes ($p < 0.05$) and the highest peak at 15 or 30 minutes following either treatment was observed. The significant changes ($p < 0.05$) last for 6 hours after the single dose, 3 hours and 4 hours after the three-doses at 5-minute and 15-minute intervals respectively. The FEV₁ was highest following the 3-doses at 15-minute intervals throughout the

6-hour study period in comparison with the other two treatments but the difference did not reach statistical significance. The mean percent changes in blood pressure, heart rate and respiratory rate are shown in Fig. 2, 3, and 4. Slightly insignificant increases in systolic blood pressure and heart rate were observed in all groups and there were no statistically significant differences among them. No difference in respiratory rate was observed.

DISCUSSION

The effective treatment of acute asthmatic attack is based on the relief of bronchoconstriction with rapid onset and few side effects. Pressurized-aerosol metered-dose inhalers are a convenient method for the



topical deposition of drugs into the airways. The extension of the mouth-piece has been shown to decrease the total loss of drug substance in the actuator and mouth and increase the amount of particles deposited in the lung.¹⁸⁻²¹ Co-ordination of the actuation of the pressurized aerosol and the inhalation becomes less important.^{26,27} The use of 750 ml spacer or tube spacer allowed greater delivery of bronchodilator to the bronchial tree than that of pressurized aerosol alone^{22,28,29} and was as effective as a higher dose used via a nebulizer.^{23, 27,30-32}

Terbutaline aerosol from a metered dose inhaler with 750 ml spacer used in this study showed a rapid onset of bronchodilatation with no serious systemic side effects, in agreement with previous studies.⁹⁻¹⁶ Greater bronchodilatation throughout the 6-hour study period following the 3-dose inhalation at 15-minute intervals was obtained. Earlier studies^{23,24} comparing the bronchodilator response of a large dose at one time with that sequential inhalations of smaller doses of the cumulative dose of terbutaline showed no difference in bronchodilating effect but both studies were done in adult patients without severe acute airway obstruction and the divided doses were given in 2 minutes in one and at 1-minute intervals in another study. The present study seems to be in agreement with a previous study in children²⁵ during acute severe airway obstruction showing that a pause of 3 minutes and 10 minutes between two puffs of terbutaline improved bronchodilatation significantly over a single dose and the greatest bronchodilatation was after two puffs at 10 minute intervals followed by two puffs at 3 minute intervals but the difference between the last two regimens did not reach statistical significance. The greater bronchodilatation observed in the longer intervals of pause presumably is a result of better penetration of aerosol into airways partially dilated

by the preceding treatment. This suggests that the pause between the inhalations at least 10-15 minutes may be necessary.

There were no significant statistical differences in blood pressure, respiratory rate, and heart rate among them. But a slight increase in heart rate was observed during the first thirty minutes. Since the two main side effects of this selective β_2 -adrenergic agonist found commonly when given orally or parenterally are skeletal muscle tremor and tachycardia,^{6,9,10,12-14,16,19,33} the use of higher dose inhalation of terbutaline must be carefully watched and titrated.

In conclusion, this present study showed that terbutaline inhalations using the 750 ml spacer of 3 doses at 15 minute intervals resulting in the greatest bronchodilatation and largest duration in comparing with the total single dose and the divided 3 doses at 5 minute intervals. There were no serious cardiovascular systemic side effects in this study.

ACKNOWLEDGEMENTS

The authors would like to thank Miss Sujitra Lertweerasirikol for her statistical analysis of the data.

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