Terbutaline in children with asthma

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Leegaard, J., and Fjulsrud, S. (1973). *Archives of Disease in Childhood*, 48, 229. **Terbutaline in children with asthma.** A double-blind, single-dose trial was carried out on 30 asthmatic children to study the effect of oral terbutaline in two different concentrations and of a placebo on ventilatory function and pulse rate. The higher dose of terbutaline (0.075 mg/kg) gave a satisfactory and prolonged action on ventilation without cardiovascular side effects.

Sympathomimetic amines have an established place in the treatment of bronchial asthma. Since the introduction of isoprenaline, a search has been undertaken for compounds with a more prolonged broncholytic action combined with fewer cardiovascular side effects. Orciprenaline was a successful result of this search (Engelhardt, Hoefke, and Wick, 1961).

Lands, Groblewski, and Brown showed in 1966, and Lands *et al.* in 1967, that there were two distinct receptors of the β -adrenergic type; the optimal structural requirements for cardiac stimulation were different from those for the advantageous broncholytic activity. After this differentiation, salbutamol was introduced, having more β_2 - and less β_1 -stimulating properties than previously known catecholamines (Hartley *et al.*, 1968; Brittain *et al.*, 1968), and about the same time terbutaline was investigated by Bergman, Persson, and Wetterlin (1969).

Terbutaline differs chemically from orciprenaline in that the N-isopropyl group is replaced by an N-tertiary butyl group. This change makes dealkylation more difficult and enhances the β -receptor stimulating properties of terbutaline.

Animal experiments have shown that terbutaline acts selectively on bronchial muscle, with little or no effect on cardiac musculature (Persson and Olsson, 1970). Clinical trials in adults (Arner, 1970; Formgren, 1970a, b; Freedman, 1971) have confirmed the pronounced and long-lasting broncholytic activity and the negligible cardiovascular side effects.

The purpose of this paper is to report a study

of the broncholytic effect and cardiovascular side effects of terbutaline, given as a single dose and in different concentrations, in asthmatic children.

Materials and methods

Patients. 10 girls and 20 boys ranging in age from 5 to 13, all suffering from moderately severe or severe bronchial asthma with symptoms from 4 to 11 years, were studied. All were in hospital because of the severity of the disease.

To be accepted into the trial a patient's peak expiratory flow rate, measured each morning of the trial, was 70% or less of the predicted normal value based on age, sex, and height (Dugdale and Moeri, 1968; Godfrey, Kamburoff, and Nairn, 1970).

At the time of the trial 4 children were receiving steroids and 3 disodium cromoglycate. All bronchodilator drugs and disodium cromoglycate were stopped 12 hours before the trial was carried out. Children receiving steroids or antibiotics continued this treatment throughout the trial period in unchanged doses.

The trial was carried out as a double-blind study on three consecutive days, a single dose of placebo and two different doses of terbutaline being given orally on separate days. One dose of terbutaline corresponded to the adult dose (0.075 mg/kg), the other dose being half this (0.0375 mg/kg). Terbutaline and placebo were administered in equal volumes as a syrup with identical smell, taste, and colour. The order in which the children received the various solutions was randomized according to the principle of Latin squares.

Respiratory function tests. Measurements were made of the peak expiratory flow rate (PEFR) using a Wright's Peak Flow Meter (Wright and McKerrow, 1959).‡

The children were all well acquainted with the technique of PEFR measurements from previous hospital stays. On the day of the trial they rested for at least 5 minutes and then three resting PEFR readings were

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Received 5 July 1972.

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TABLE
Peak expiratory flow

	Initial value		Difference after 1 hr			t_0
	No.	M	No.	M	$\pm$ SEM	
Terbutaline 0.075 mg/kg (A)	24	162	24	+38.8	5.88	6.59
Terbutaline 0.0375 mg/kg (B)	27	158	27	+14.3	4.70	3.03
Placebo (C)	26	153	26	+3.7	3.74	0.98
Difference between difference						
Dose A/dose C			23			5.92
Dose B/dose C			25			1.70
Dose A/dose B			24			3.34

No., number of patients; M, mean of individual changes from initial value; SEM, standard error of the mean; t_0 , difference between the

recorded. The solution was given and PEFR measurements were made at 1, 2, 3, and 5 hours. On each occasion three PEFR values were obtained and the highest value recorded.

Pulse rate. The pulse rate was measured by palpation of the radial artery for 1 minute immediately before each PEFR measurement.

Side effects. Notes were taken of any spontaneous remarks by the children relating to their symptoms after taking the solutions. After 5 hours the children were asked if they had noticed any symptoms such as tremor, palpitation, headache, or sweating.

Statistics. Student's 't' test (Mainland, 1963; Snedecor and Cochran, 1967) was used for evaluation of the results, the degree of significance being given as significant ($P < 0.01$), or highly significant ($P < 0.001$).

Results

Airway obstruction. The lower dose of terbutaline had a significant effect after 1 hour, and a highly significant effect after 2 and 3 hours (Table I, Fig. 1). The effect after the higher dose was highly significant after the first 3 hours, and significant after 5 hours (Table I, Fig. 1).

The difference in effect between the high dose

of terbutaline and placebo was highly significant after the first 3 hours, and significant after 5 hours. Between the lower dose and placebo the difference was highly significant after 3 hours. Between the two doses of terbutaline the difference was significant after 1 and 2 hours (Table I).

FIG. 1.—Mean of individual changes in peak expiratory flow rate from the initial value after oral administration of two doses of terbutaline and placebo. Bars represent ± 1 SD.

TABLE
Pulse rate

	Initial value		Difference after 1 hr			t_0
	No.	M	No.	M	$\pm$ SEM	
Terbutaline 0.075 mg/kg (A)	29	94	29	-0.9	2.11	0.42
Terbutaline 0.0375 mg/kg (B)	30	89	30	+1.8	2.19	0.82
Placebo (C)	30	90	30	+0.3	2.30	0.14
Difference between difference*						
Dose A/dose C			29			0.42
Dose B/dose C			30			0.44
Dose A/dose B			29			1.07

No., number of patients; M, mean of individual changes from initial value; SEM, standard error of the mean; t_0 , difference between the

rate (l./min)

Difference after 2 hr				Difference after 3 hr				Difference after 5 hr			
No.	M	± SEM	t ₀	No.	M	± SEM	t ₀	No.	M	± SEM	t ₀
24	+55.0	7.01	7.84*	24	+49.0	7.48	6.55*	21	+23.1	6.98	3.31†
27	+27.6	7.14	3.87*	27	+29.6	6.31	4.70*	24	—0.8	6.25	0.13
26	+5.6	6.21	0.89	26	—2.3	6.09	0.38	25	—3.0	7.10	0.42
23			6.08*	23			6.47*	19			3.87†
25			2.78	25			4.34*	21			0.59
24			3.33†	24			2.33	20			2.50

hieved with the different solutions.

*P < 0.001.

†P < 0.01.

Pulse rate. The rise in pulse rate was almost significant after 2 hours using the high dose of terbutaline. Otherwise there were no changes in pulse rate at any time using any of the solutions (Table II, Fig. 2).

FIG. 2.—Mean of individual changes in heart rate from the initial value after oral administration of two doses of terbutaline and placebo. Bars represent ± 1 SD.

Side effects. No side effects were noted at any time during or after the trial.

Discussion

The results show that orally administered terbutaline in the concentrations used produces marked bronchodilatation in asthmatic children for a period of at least 5 hours without tachycardia.

The mean maximal PEFR increase after the lower dose of terbutaline was no better than 60% of the increase after the high dose at any time. Table I shows that this difference in effect was significant for the first 2 hours. This ventilatory advantage indicates that the high dose (which corresponds to the adult dose) is to be preferred to the lower when given as a single dose.

The observed changes in heart rate show that the higher dose exerts some activity on the β_1 -receptors. The mean maximal increase was 5 beats per minute after the higher dose. This corresponds well with the results of investigations in adults (Formgren, 1970a), but is in contrast to that of Freedman (1971) who found a much higher heart rate increase.

It is possible that an even greater degree of

beats/min)

Difference after 2 hr			Difference after 3 hr			Difference after 5 hr					
No.	M	± SEM	t ₀	No.	M	± SEM	t ₀	No.	M	± SEM	t ₀
29	+5.0	2.10	2.37	29	+1.3	2.21	0.59	26	±0.0	2.10	0.00
30	+4.5	2.30	1.94	30	+1.4	2.30	0.64	28	+0.4	2.58	0.14
30	+1.6	2.53	0.66	30	—0.3	2.74	0.12	29	—2.1	2.15	0.96
29			0.97	29			0.28	25			0.91
30			0.80	30			0.49	27			0.82
29			0.12	29			0.07	26			0.39

hieved with the different solutions.

*None of the differences is significant.

bronchodilatation could have been achieved using a higher concentration of terbutaline, but probably at the cost of some tachycardia.

In conclusion, the ventilatory benefits combined with no cardiovascular side effects makes terbutaline a safe and effective broncholytic agent when given as a single dose and in a concentration of 0.075 mg/kg body weight.

We thank Dr. K. Aas for permission to investigate patients under his care and for his advice concerning the trial and preparing the manuscript; nurses Anne Kasin and Valborg Lachman-Mørch for technical assistance; and DRACO AB for supplying the samples and carrying out the statistical analyses.

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