

## No protection by oral terbutaline against exercise-induced asthma in children: a dose-response study

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*No protection by oral terbutaline against exercise-induced asthma in children: a dose-response study. G. Fuglsang, B. Hertz, E-B. Holm. ©ERS Journals Ltd 1993.*

**ABSTRACT:** We wanted to assess the protective effects on exercise-induced asthma as well as the clinical efficacy and safety of increasing doses of a new sustained-release formulation of terbutaline sulphate, in 17 asthmatic children aged 6-12 yrs (mean 9 yrs). Placebo, 2, 4 and 6 mg terbutaline were given *b.i.d.* for 14 days, in a randomized, double-blind, cross-over design. At the end of each two week period, an exercise test was performed and plasma terbutaline was measured.

Compared with placebo, no significant effect was seen on asthma symptoms monitored at home, or on exercise-induced asthma. The percentage falls in FEV<sub>1</sub> after the exercise test were 36, 35, 27 and 28%, after placebo, 4, 8 and 12 mg terbutaline·day<sup>-1</sup>, respectively. There was no correlation between plasma terbutaline and dose of terbutaline. A small but statistically significant dose-related increase in morning and evening peak expiratory flow (PEF) recordings occurred, but the incidence of side-effects also increased with the dose given. There was a trend towards more side-effects when the high doses were used, and two patients withdrew from the study because of side-effects at this dose.

It is concluded that continuous treatment, even with high doses of oral terbutaline, does not offer clinically useful protection against exercise-induced asthma.

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Exercise-induced asthma (EIA) is common in asthmatic children. It is well-known that inhalation therapy with a beta<sub>2</sub>-adrenoceptor agonist prevents EIA both in children and in adults, so that the fall in lung function is reduced to less than 10% in most patients. In contrast, the protective effect of oral treatment with beta<sub>2</sub>-adrenoceptor agonists against EIA is controversial. Some studies have found little effect of oral agents [1, 2] compared with the aerosol formulation, whilst others have concluded that oral treatment with a beta<sub>2</sub>-agonist does protect against EIA. [3, 4]. Most studies have used single doses, 1-2 h before exercise. To our knowledge, the protective effect of regular treatment with an oral beta<sub>2</sub>-agonist has not previously been investigated in a double-blind, dose-response study in children.

Many children do not, or do not wish to, inhale a beta<sub>2</sub>-agonist just prior to exercise. Instead, they refrain from vigorous exercise or stop exercising when they feel their asthma attack coming on. We wished to investigate if oral treatment with slow-release terbutaline in high doses offers any clinically useful protection against EIA. Therefore, the aim of the present study was to evaluate the protective effect of oral terbutaline against EIA, and the safety of increasing doses.

### Patients and methods

Twenty one patients were included in the study. Four were excluded in the first or second treatment period. The reasons for exclusion were: deterioration of asthma (2), side-effects (1) and poor compliance (1).

The remaining children, 11 boys and 6 girls, completed the study. Their ages were 6-12 yrs (mean 9 yrs), and their body weight 24-47 kg (mean 32 kg).

There were three inclusion criteria: 1) all suffered from mild or moderate asthma; 2) all had a reversibility >15% in peak expiratory flow rate (PEF) after inhalation of 0.5 mg terbutaline; and 3) in the two weeks prior to the study, the children had been tested for exercise-induced asthma (EIA) with a positive result. Only data from children who also had a >15% fall in FEV<sub>1</sub> after exercise during placebo treatment were included in the analysis of the effect on EIA.

Apart from inhaled beta<sub>2</sub>-agonist *p.r.n.* eight patients were treated with sodium cromoglycate (Lomudal or Lomuforte), one with oral antihistamine (Teldanex), and one with inhaled nasal steroid (Beconase Aqua). Concomitant medication was kept constant throughout the study, and for at least two weeks before entry. Sodium

cromoglycate or inhaled beta<sub>2</sub>-agonist was not inhaled less than 5 h before the exercise tests.

None of the patients had ongoing airway infection or seasonal allergy. Informed consent was obtained from all children and their parents, and the study was approved by the local Ethics Committee.

The design was a randomized, double-blind, cross-over, dose-response study. Three doses of terbutaline: 2, 4 and 6 mg *b.i.d.*, and placebo, were given for four 2 week periods.

A new terbutaline sustained release (SR) formulation was used. It consists of granules in capsules, which can be sprinkled onto a spoon with soft food. Twice daily dosing with this formulation has been shown to be effective [5], and to give stable plasma concentrations (Börgstrom, unpublished data). The maximum concentration was measured 4.5 h (range 2.2–6.0 h) after the administration [6].

During each treatment period, the patients used diaries every morning and evening. The following data were recorded: PEF measured with a Mini-Wright peak flow meter every morning and evening just prior to oral terbutaline medication, and asthma symptoms scored on a 4 point scale: 0 = none, 1 = mild, 2 = moderate and 3 = severe. In addition, the use of rescue medicine: inhalations of terbutaline (0.25 mg per dose), and possible side-effects such as tremor, headache, palpitations and uneasiness were recorded. At the end of each treatment period the patients were clinically evaluated with lung function, pulse rate and tremor. The children visited the clinic at the same time of the afternoon 6±1 h after morning medication. A blood sample was drawn to measure plasma terbutaline, and an exercise test was performed half an hour later. Terbutaline in plasma was measured by gas chromatography-mass spectrometry (GC-MS).

The exercise test was performed as follows: the children ran on a treadmill for 6 min, the load being kept constant at 80–90% of the child's maximal workload, so that the heart rate was at least 180 beats·min<sup>-1</sup> at the end of the test. Heart rate was monitored by telemetry during the test. The ambient temperature and the relative humidity of the room were recorded. FEV<sub>1</sub> was measured on a dry wedge spirometer, (Vitalograph, UK) immediately before the exercise (baseline value), immediately after, and 3, 5, 10, 15 and 20 min after the run. The highest value of three was recorded. The children did not wear a noseclip during the exercise test, but they were instructed to breathe through the mouth. The exercise-induced fall in FEV<sub>1</sub> was expressed as follows:

$$\% \text{ fall in FEV}_1 = \frac{\text{Baseline FEV}_1 - \text{lowest FEV}_1 \text{ after exercise}}{\text{Baseline FEV}_1} \times 100$$

The protection against EIA afforded by terbutaline was calculated as the % reduction in EIA on the various active treatment days (EIAa), as compared to the individual EIA on the placebo day (EIAp):

$$\% \text{ protection} = \frac{\% \text{ fall placebo} - \% \text{ fall active}}{\% \text{ fall placebo}} \times 100$$

#### Statistics

The comparisons between the four treatments (placebo, terbutaline 2 mg *b.i.d.*, terbutaline 4 mg *b.i.d.*, and terbutaline 6 mg *b.i.d.*) are based on an analysis of variance (ANOVA) model, with the factors patient, treatment and period, and the dose-response was assessed as the component of linear regression on dose.

Table 1. — Plasma terbutaline levels, FEV<sub>1</sub> and heart rate, before and after exercise maximum % fall in FEV<sub>1</sub> after exercise, and ambient conditions during exercise, in 12 children with exercise-induced asthma, treated with placebo, 2, 4 and 6 mg terbutaline *b.i.d.*

	Terbutaline mg·day <sup>-1</sup>				
	0	4	8	12	
Plasma terbutaline nmol·l <sup>-1</sup>	1.0 (0.5–2)	11.5 (5–18)	22.8 (10–41)	23.1 (10–37)	
Baseline FEV <sub>1</sub> l	1.69±0.5	1.67±0.4	1.71±0.4	1.70±0.4	NS
% fall in FEV <sub>1</sub>	36±18	35±16	27±16	28±22	NS
Maximal FEV <sub>1</sub> l	1.88±0.4	1.89±0.4	1.86±0.4	1.84±0.4	NS
Heart rate pre-exercise beats·min <sup>-1</sup>	94±10	97±14	96±10	98±12	NS
Heart rate postexercise beats·min <sup>-1</sup>	182±7	183±6	187±7	184±8	NS
Relative humidity %	54.3	54.5	55.0	55.5	NS
Temperature °C	22.3	22.2	22.3	22.3	NS

Each treatment period was 14 days, and the exercise test was carried out on the last day in each period. Values are given as mean±sd, except for plasma terbutaline, which is given as mean and range in parenthesis. The mean predicted value for FEV<sub>1</sub> is 1.91 l. FEV<sub>1</sub>: forced expiratory volume in one second; ns: nonsignificant.

## Results

Seventeen patients completed the study and the data from the diaries are statistically analysed for this group.

When the effect of terbutaline granulate on EIA was analysed, it was found that five children failed to fulfil the criteria of >15% fall in FEV<sub>1</sub> during the placebo period. Therefore, only data from the 12 remaining children were used when the effect on EIA was evaluated.

### EIA and plasma terbutaline: 12 patients

Marked interindividual variations in plasma terbutaline on the same doses of terbutaline were seen (table 1).

Baseline FEV<sub>1</sub> measured before the exercise test and percentage fall in FEV<sub>1</sub> after exercise were not significantly affected by the terbutaline treatment (table 1). There was no significant correlation between plasma terbutaline and percentage fall in FEV<sub>1</sub> (fig. 1).

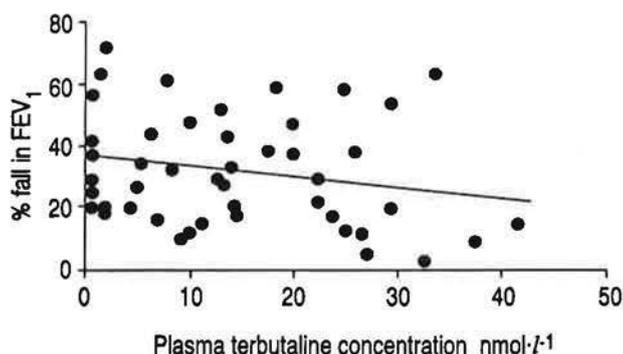


Fig. 1. - Percentage fall in FEV<sub>1</sub> after exercise in relation to plasma terbutaline measured immediately before the test, in 12 children treated with slow release oral terbutaline 2, 4 and 6 mg *b.i.d.* There was no statistically significant correlation between plasma terbutaline and percentage fall after exercise. FEV<sub>1</sub>: forced expiratory volume in one second.

However, when the percentage fall in FEV<sub>1</sub> after exercise during placebo was compared with the percentage fall during the period where the highest plasma terbutaline concentration was measured, it was found that the high concentrations were associated with a significant reduction in EIA: 36% (placebo) and 26% (high dose)  $p < 0.02$ . In five patients, the protection was >50% (plasma levels 22–37 nmol.l<sup>-1</sup>). The mean highest plasma terbutaline concentration for all 12 patients was 28 nmol.l<sup>-1</sup> (Range 22–41 nmol.l<sup>-1</sup>).

### Diary recordings and side-effects: 17 patients

The severity of asthma was generally scored as mild to moderate, and there was no significant difference between the four periods. However, a statistically significant dose-response was observed in PEF measured in the morning and in the evenings (table 2).

## Discussion

The main aim of the study was to evaluate the influence of steady-state oral terbutaline treatment on exercise-induced asthma. Therefore, we selected patients with mild and moderate stable asthma, whose pulmonary functions were close to normal. This would increase the likelihood of a stable baseline pulmonary function during the study, and facilitate the interpretation of the results from the exercise tests. Therefore, it was difficult to demonstrate marked differences in the children's clinical condition. Only PEF recordings in the morning and evening showed dose-related variations.

Although there was no correlation between terbutaline dose and protection against EIA, we found that the highest plasma level of terbutaline had a statistically significant effect on EIA. We have to conclude, however, that the clinical effect of oral terbutaline on exercise-induced asthma is insufficient, as the mean percentage fall in FEV<sub>1</sub> even at the highest obtained plasma concentrations, was still 26%.

Table 2. - Peak expiratory flow rate (PEF), symptom scores and use of rescue inhaler terbutaline, in 17 children with asthma, treated with placebo, 2, 4 and 6 mg slow release oral terbutaline *b.i.d.*

	Terbutaline mg·day <sup>-1</sup>				0 vs 12
	0	4	8	12	
PEF morning l·min <sup>-1</sup>	241±63	243±58	250±66	258±64	p<0.002
PEF evening l·min <sup>-1</sup>	255±68	265±60	266±69	276±65	p<0.007
Day symptoms score 0–3	0.15 (0–2.4)	0.22 (0–2.2)	0 (0–2.5)	0.11 (0–2.0)	NS
Night symptoms score 0–3	0.49 (0–2)	0.20 (0–2)	0.11 (0–1.4)	0.20 (0–2.1)	NS
Rescue terbutaline inhalation n	0.5 (0–3.3)	0.5 (0–3.1)	0.5 (0–3.2)	0.5 (0–3.1)	NS

Each treatment period was 14 days. Morning and evening PEF are given as mean±SD, symptoms and use of rescue terbutaline as median and range. The mean predicted PEF is 300 l·min<sup>-1</sup>. NS: nonsignificant.

The lack of a clinically important effect could not be ascribed to a low degree of EIA in the patients studied. The mean fall in FEV<sub>1</sub> after placebo was 36%. At the highest dose, there was still room for further improvement, indicating that the top of the dose-response curve had not been reached, even at plasma terbutaline levels around 28 nmol·l<sup>-1</sup>. To our knowledge, terbutaline has no generally accepted therapeutic range. However, in an earlier *i.v.* dose-response study [7] on children with acute bronchoconstriction, we found that maximum bronchodilator effect was achieved at plasma terbutaline levels around 30 nmol·l<sup>-1</sup> (range 20–60 nmol·l<sup>-1</sup>).

In good agreement with these findings, only the highest plasma levels (23–28 nmol·l<sup>-1</sup>) produced a significant effect in the present study. The levels that produced maximum effect were associated with side-effects such as tremor in all patients. Therefore, it is most unlikely that we could have increased the dose further in the present study.

In conclusion, continuous treatment with oral terbutaline does not offer effective protection against exercise-induced asthma in children, but the treatment is clinically effective in improving peak expiratory flow rate.

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