

Cumulative dose response relationship of terbutaline delivered by three different inhalers

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In a controlled, open cross-over study 15 asthmatic children received increasing doses of terbutaline (0.125 mg + 0.125 mg + 0.25 mg + 0.5 mg + 0.1 mg) delivered by a pressurized aerosol alone or with a tube spacer or a nebulizer attached. At no time was there any significant difference in measured FEV_1 or percent increase in FEV_1 between the three inhalers. However, when eight patients with bronchodilation > 50% on all tests days were studied separately, a significantly greater improvement in FEV_1 was seen after the first three inhalations of terbutaline when a nebulizer or a tube spacer was used compared with the response after the pressurized aerosol ($P < 0.05$). Bronchodilation measurements did not differ after use of the two spacers. There was no statistically significant difference in side effects between the three inhalers, but there was a trend towards a higher occurrence of side effects when the pressurized aerosol was used alone.

Key words: asthma; children; dose response; nebulizer; pressurized aerosol; tube-spacer.

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CLINICAL ASPECTS

The normally recommended dose of 0.5 mg terbutaline is suitable for children receiving inhaled therapy with pressurized aerosols. When used correctly there seems to be little difference between the bronchodilating effect of a pressurized aerosol alone, and a pressurized aerosol with a spacer system attached. Only in patients with highly reversible asthma can a significant beneficial effect from the spacers be demonstrated.

Dose response studies with inhaled drugs and evaluations of inhalation techniques are usually carried out on adult asthmatic patients. The conclusions from such studies are normally assumed to be clinically relevant also in children and therefore the same drug doses and the same inhalation techniques are used in both children and adults. However, as airway calibre and anatomy of the upper airways differ in children and adults, and it is not known whether the density and distribution of receptors within the airways are similar in the two groups, extrapolating results from adult studies to children is inadvisable.

We performed the present study in asthmatic children to evaluate the dose-response relationship of inhaled accumulated doses of terbutaline

delivered by an ordinary pressurized aerosol (PA) and a PA with two different spacer systems attached.

PATIENTS AND METHODS

Eleven boys and four girls aged 6-15 years (mean 10 years) participated in the study. All suffered from chronic asthma associated with an increase in forced expiratory volume in one second (FEV_1) of at least 20% after 2 puffs of terbutaline. The patients were all well trained in the inhalation technique. Informed consent was obtained from all patients and their parents and the study was approved by the Ethics Committee of northern Jutland.

The design was that of a controlled, open

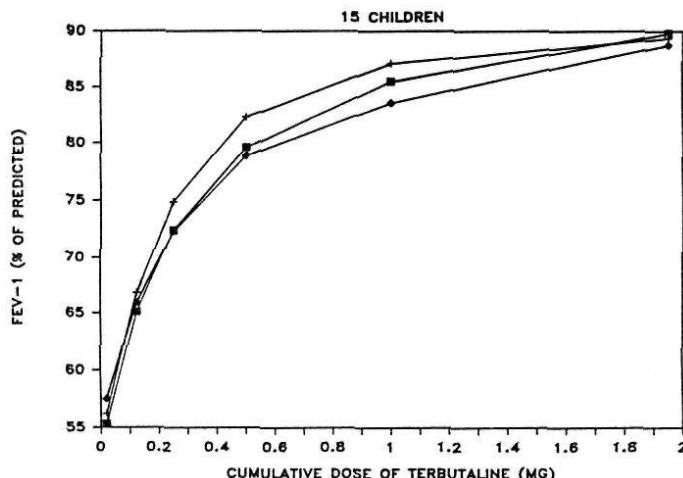


Fig. 1. FEV₁ in percentage of predicted in 15 asthmatic children receiving increasing doses of inhaled terbutaline delivered from a presurized aerosol (♦), a pressurized aerosol with a 10 × 3.2 cm tube spacer (+), and a pressurized aerosol with a nebulizer (■).

cross-over study in which the children on 4 separate days received, in randomised sequence, accumulated doses of terbutaline delivered by:

- 1) an ordinary pressurized aerosol
- 2) a PA with a straight 10 × 3.2 cm tube spacer (TS)
- 3) a PA with a pear-shaped spacer with a volume of 750 ml and mouthpiece with a one-way valve system (Nebuhaler = NEB)
- 4) placebo (delivered by the nebulizer).

On all study days the following doses of terbutaline (or placebo) were given with 20-min intervals: 0.125 mg, 0.125 mg, 0.25 mg, 0.5 mg and 1.0 mg; the accumulated dose on each day being 2.0 mg.

The results from a patient were only evaluated if pretreatment FEV₁ was < 70% of the predicted value (8) on all 4 test days and if the variation in pretreatment FEV₁ between the various days was < 15%. The children were allowed to use inhaled beta₂-agonists up to 6 h before each study day. Treatment with all other drugs was stopped 48 h prior to the test days.

FEV₁ was measured on a dry wedge spirometer (Vitalograph) immediately before the first treatment and then 20 min after each inhala-

tion. In addition, measurements were made 1, 1.5, and 2 h after the last inhalation. The highest of three recordings was used. Pulse rate and the occurrence of tremor (0 = no, 1 = slight, 2 = moderate, 3 = severe) were recorded at the same times as FEV₁.

Statistics

Analysis of variance was used to compare the results from the various treatments. A *P*-value < 0.05 was considered statistically significant.

RESULTS

FEV₁ after the various treatments is shown in Fig. 1. There was no statistically significant difference between baseline pulmonary functions on the 4 test days. Pretreatment FEV₁ varied from 41% to 68% of predicted (mean 56.4%). Mean pretreatment FEV₁ being 1.28/l (range 0.52–2.30). Compared with placebo, all active treatments resulted in a significant bronchodilation throughout the whole study period. The mean total increase in FEV₁ was the same on all 3 days of terbutaline administration (56%; range 25–92% (PA), 61%; range 26–110% (TS) and 64%; range 34–106% (NEB)) and at no time was

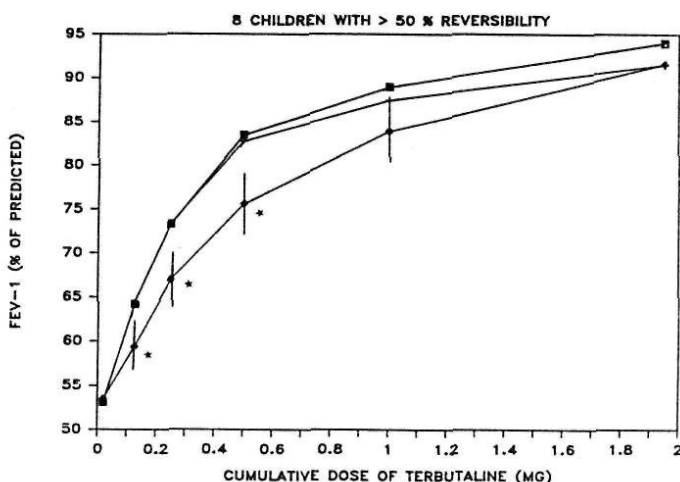


Fig. 2. FEV_1 in percentage of predicted in eight asthmatic children with a reversibility of more than 50% in FEV_1 . The children received increasing doses of inhaled terbutaline delivered from a pressurized aerosol (◆), a pressurized aerosol with a 10 × 3.2 cm tube spacer (+), and a pressurized aerosol with a nebulizer (■), * $P < 0.05$.

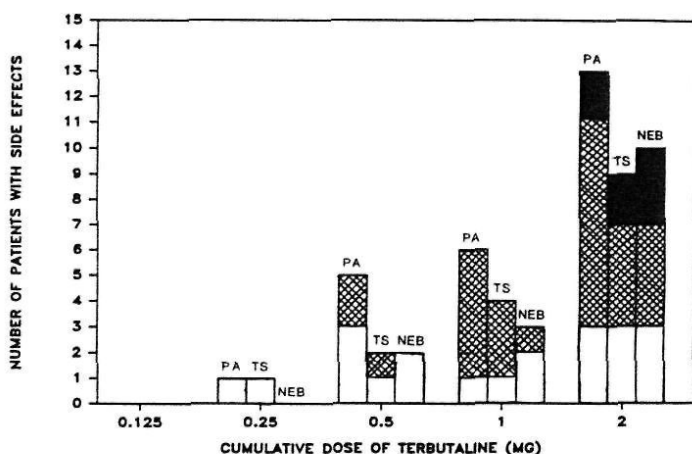


Fig. 3. Occurrence of side effects in 15 asthmatic children receiving increasing doses of inhaled terbutaline delivered from a pressurized aerosol, a pressurized aerosol with a 10 × 3.2 cm tube spacer and a pressurized aerosol with a nebulizer. □ = light tremor, ▨ = moderate tremor, ■ = severe tremor

there any significant difference in measured FEV_1 or per cent increase in FEV_1 between the three inhalers. Mean FEV_1 after the three treatments was 1.95/l (range 0.90–3.20), 1.94/l (range 0.96–3.0) and 1.95/l (range 0.96–3.6) for PA, TS and NEB respectively. A small but statistically significant change in FEV_1 of 5% was seen after placebo treatment ($P < 0.05$).

Eight patients showed a bronchodilation > 50% on all 3 active test days (age = 6 to 11 years; mean 8 years). The results from these patients are shown in Fig. 2. Neither in this group was there any statistically significant difference in pretreatment FEV_1 on the 3 active treatment days; this parameter varying from 41 to 68% (mean 53.3%) of predicted (equivalent

to 0.52/l and 1.45/l). However, a significantly greater bronchodilation was seen after the three first inhalations of terbutaline (accumulated dose = 0.5 mg) when a TS or a NEB was used compared with the response after the PA ($P < 0.05$). After this treatment there was no significant difference between the three inhalers. The mean total increase in FEV₁ after the three inhalers being 71 % (PA), 74 % (TS), and 79 % (NEB).

There were no significant changes in pulse rate on any of the study days. The occurrence of tremor on the 3 days of terbutaline treatment is shown in Fig. 3. Though not statistically significant, there was a trend towards a higher frequency of tremor when the PA was used.

DISCUSSION

The therapeutic effect of inhaled bronchodilators depends upon the amount of inhaled drug deposited in the lungs and its distribution within the airways. Compared with the results from PA, Newman (6) found a significant enhancement in the intrapulmonary deposition of radioactively labelled teflon particles when a TS or NEB was used. In accordance with this, Lindgren, Pauwels and Cushley (1, 3, 7) all found that the attachment of a spacer device did increase bronchodilation in adults with asthma. The cumulative dose of terbutaline in these studies varied from 1.5–4 mg. However, other dose-response studies on adults have not been able to detect any benefit from the addition of a TS or NEB to a PA (2, 5). In these studies the cumulative dose of terbutaline was 0.5 mg. The discrepancy between these results is not clear. The studies differed in design, dose used, number of patients and perhaps also in degree of airway reversibility.

In the present study we only included children with a high reversibility and an optimal inhalation technique. This should increase the likelihood of detecting a difference in bronchodilation between the three devices. Yet there was no difference in bronchodilation between the three inhalers (Fig. 1). However, in the most reversible (and most obstructed) patients a significant beneficial effect of the spacers was

found in the normally recommended dose range (Fig. 2). We do not know the reason for this. It may merely reflect the fact that a difference in pulmonary deposition of drug was easier to detect in these patients because they were at the lower end of the dose-response curve when entering the study. Another possible factor could be the lower age in this group. The upper airway anatomy in younger children is different from that of older children. The narrow passage in a young child increases the likelihood of turbulence and drug impaction. Since the particles from a PA are larger and have a higher velocity at the time they reach the patient (6), drug impaction may be more pronounced with this inhaler than with a spacer device in young children.

In all patients 0.5 mg of inhaled terbutaline resulted in satisfactory bronchodilation with few side effects. Increasing the dose from 0.5 mg to 1 or 2 mg only improved pulmonary functions 7 % and 11 % respectively. This additional improvement was achieved at the expense of a much higher occurrence of unpleasant side effects. Therefore, 0.5 mg inhaled terbutaline seems a suitable dose in the day-to-day treatment of children with asthma.

The apparently higher incidence of side effects with PA could have been a coincidence, but it may also have been due to systemic absorption of drug deposited in the oral cavity by impaction. This would be in agreement with the results of Newman and others (4, 6), who found that spacers reduce the oral deposition of aerosol particles.

Conclusion

The normally recommended dose of 0.5 mg terbutaline is suitable for children receiving inhaled therapy with pressurized aerosols. When used correctly there is little difference between the effect of a PA, a TS and an NEB.

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