

Bronchodilation of Terbutaline in Small Doses from a 750 ml Spacer

A Cumulative Dose-Response Study

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The influence on lung function of small cumulative doses (31 + 31 + 63 + 125 + 250 µg) of terbutaline inhalations from a pressurized aerosol with a 750 ml spacer was evaluated in 12 stable asthmatics. The trial was double-blind and cross-over, using the double-dummy method. Lung functions was recorded 5, 30, and 60 min after each inhalation. No significant differences in FEV₁, FVC and FMF_{25-75%} were found between the two devices. A very marked response, which was not a placebo effect, was noted after the subjects had inhaled the first 31 µg dose. The results suggest that the number of inhalations is more important for the response in lung function than the dose administered. The addition of a 750 ml spacer to the pressurized aerosol is not likely to be beneficial for adults who are able to handle an ordinary aerosol properly.

Key words: aerosol; dose-response; spacer; terbutaline.

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In bronchodilator therapy the inhaled route has advantages over other routes of administration. The onset of action is more rapid and the same bronchodilating effect is obtained with much smaller doses than in oral ingestion therapy; this minimizes the risks of side effects (5). Among the disadvantages are the requirement for patient compliance and the fact that only 10%, or less, of the aerosol is deposited in the intrathoracic airways, even with the correct use of a pressurized aerosol (9). These drawbacks may to some extent be eliminated by the use of an extension device connected to the actuator of the pressurized aerosol. By the interposition of a spacer device the velocity and size of the aerosol particles may be reduced and an aerosol obtained that is more suitable for deposition of particles in the intrathoracic airways (8).

We report the effects on lung function produced by a pressurized terbutaline aerosol in small doses, administered via a 750 ml spacer.

MATERIAL AND METHODS

Patients

A total of 19 patients (11 males, 8 females) participated in the study. Their mean age was 39 years (range 24-57 years) and their mean 1 sec forced expiratory volume (FEV₁) was 66% (range 24-106%) of the predicted normal value. All patients had bronchial asthma and showed a mean increase of 39% (range 23-100%) in FEV₁ 30 min after inhalation of 0.160 mg isoprenaline 1 day before the study started. The patients were in a stable phase of their disease and their baseline FEV₁ values on the 2 days of the study did not vary more than 15% from the lowest value.

All patients took oral and/or inhaled β₂-agonists daily and seven of them took theophylline preparations. Steroids were inhaled by 12 patients and taken orally by four. Treatment with β₂-agonists and theophylline was dis-

continued 8 h and 24 h, respectively, before the study. Steroids and other medications were kept constant on the days of the study.

Design

The study was divided into two parts, with 12 patients participating in each. Part I was a randomized double-blind, 2-day, cross-over study, using the double-dummy method. On one of the days the patients inhaled the active drug via the ordinary actuator and the placebo via the 750 ml spacer. On the other day the patients inhaled the active drug via the 750 ml spacer and the placebo via the ordinary actuator. The order, active drug – placebo, or placebo – active drug, was randomized but kept the same for each individual during the 2 days of the experiment. The patients inhaled 31, 31, 63, 125, and 250 μ g of terbutaline in a single dose sequence from specially-prepared pressurized aerosols (AB Draco, a subsidiary of AB Astra, Sweden).

In part II, the patients inhaled placebo, 31 μ g and 250 μ g of terbutaline from the ordinary actuator or the 750 ml spacer. Part II was performed single-blind as regards the dose sequence, while it was open with regard to the device. The device sequence for the 2 test days was randomized.

Recordings of FEV₁ and forced vital capacity (FVC) were performed with a dry wedge spirometer (Vitalograph Ltd.), and the forced mean expiratory flow over the middle half of the forced vital capacity (FME_{25–75%}) was calculated from the spiograms. FME_{25–75%} after inhalation was adjusted to the same segment as before inhalation (FME_{25–75% corr.}) (12). The best of three forced expirations was used.

The studies started each day at 9 a.m., following a rest of 15 min. After recording of the basal lung function values, the inhalations were made at 60-min intervals.

The lung function was recorded 5, 30, and 60 min after inhalation of each dose. In part II, after 250 μ g of terbutaline, additional recordings were made at 120 min.

Each day of the trial concluded with the inhalation of 2×80 μ g isoprenaline, followed by

lung function recordings 5 min later to ensure that the patients had not reached their maximum value.

Mode of inhalation

Ordinary actuator: the patients were instructed to inhale slowly from a residual volume to total lung capacity, with a breath-holding pause “as long as possible”. The actuator was fired in the beginning of an inhalation.

750 ml spacer: the patients were instructed to release one puff into the spacer and immediately afterwards to empty the spacer with 2–3 deep and slow inhalations from the residual volume.

In part II of the study, inhalation was performed in one deep breath and a breath-holding pause of 10 sec with both inhalation methods.

Statistics

The Student's t-test for paired observations was used and differences were considered significant for values of $P < 0.05$.

RESULTS

Part I

The baseline values in FEV₁ for the 2 days were 2.02 ± 0.19 l (mean $\pm$ SEM) with the ordinary actuator and 2.04 ± 0.20 l with the 750 ml spacer. The individual variations between the 2 days were 2–15% (mean 9.3%). There were significant increases in FEV₁, FVC and FME_{25–75% corr.} from 5 min after the first dose (31 μ g) and after all further doses compared to the baseline values with both devices.

There were no significant differences after any of the doses or at any of the times in FEV₁ and FVC, while significant differences ($P < 0.05$) were noted in FME_{25–75% corr.} at 210, 240, and 270 min in favour of the ordinary actuator (Fig. 1). There was a further significant increase in FEV₁ after 2×80 μ g isoprenaline ($P < 0.05$).

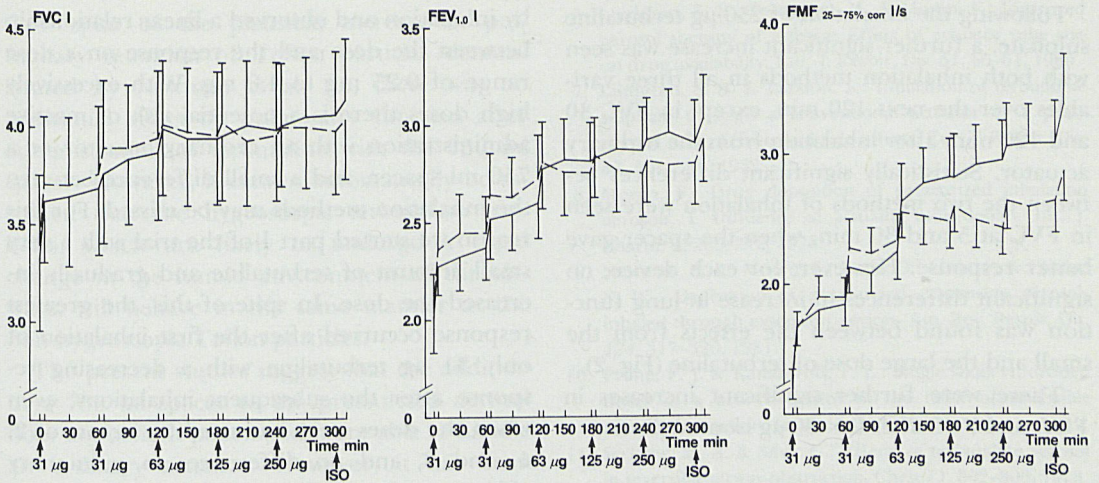


Fig. 1. Effects on FVC, FEV₁ and FMF_{25-75% corr.} of increasing doses of terbutaline. At 300 min two puffs of isoprenaline (2 × 80 µg) were inhaled. The unbroken line indicates the ordinary actuator and the broken line indicates the 750 ml spacer. The vertical lines correspond to the SEM.

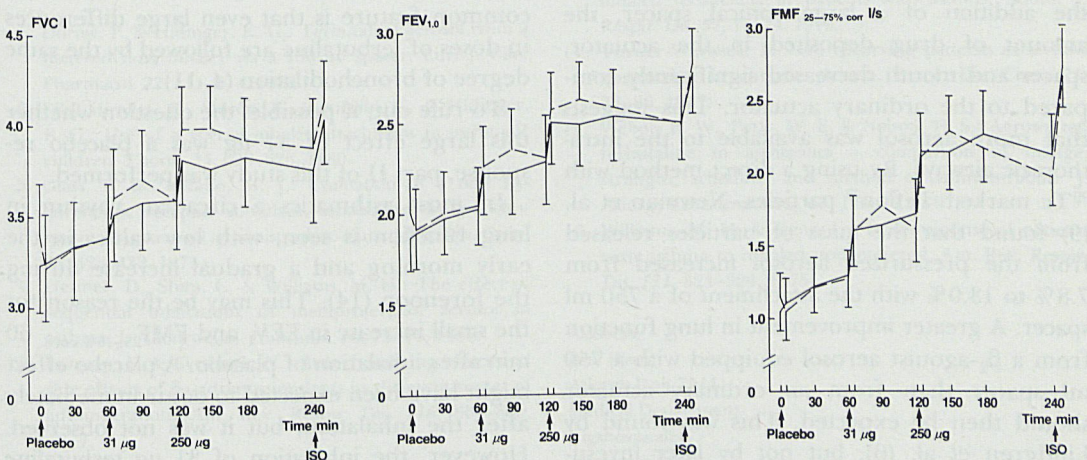


Fig. 2. Effects on FVC, FEV₁ and FMF_{25-75% corr.} of placebo, 31 µg and 250 µg terbutaline sulphate. At 240 min two puffs of isoprenaline (2 × 80 µg) were inhaled from an ordinary actuator on both days. The unbroken line indicates the ordinary actuator and the broken line indicates the 750 ml spacer. The vertical lines correspond to the SEM.

Part II

The baseline values in FEV₁ before the placebo for the 2 days were 1.87 ± 0.18 l (mean $\pm$ SEM) with the ordinary actuator and 2.01 ± 0.22 l with the 750 ml spacer, which meant a statistically significant difference ($P < 0.05$). After inhalation of the placebo the FEV₁ recordings were 2.03 ± 0.20 l and 2.05 ± 0.21 l, respective-

ly. The individual variability between the 2 days was 0–19% (mean 7.2%) after the placebo. A significant increase over the baseline values recorded after the placebo was seen in all variables, FEV₁, FVC, and FMF_{25-75% corr.}, at all times following the inhalation of 31 µg terbutaline sulphate, except in the FVC 5 min after inhalation from the ordinary actuator.

Following the inhalation of 250 µg terbutaline sulphate, a further significant increase was seen with both inhalation methods in all three variables over the next 120 min, except in FVC 30 and 120 min, after inhalation from the ordinary actuator. Statistically significant differences between the two methods of inhalation were seen in FVC at 5 and 30 min, when the spacer gave better response. However, for each device, no significant differences in increase in lung function was found between the effects from the small and the large dose of terbutaline (Fig. 2).

There were further significant increases in FEV₁ and FVC after 2 × 80 µg isoprenaline.

DISCUSSION

In a study on the retention of terbutaline in normal volunteers, Morén (8) showed that, with the addition of a large conical spacer, the amount of drug deposited in the actuator, spacer and mouth decreased significantly compared to the ordinary actuator. This suggests that more aerosol was available to the intrathoracic airways. By using a direct method with ⁹⁹Tc marked Teflon® particles, Newman et al. (9) found that the mass of particles released from the pressurized aerosol increased from 7.8% to 13.0% with the attachment of a 750 ml spacer. A greater improvement in lung function from a β₂-agonist aerosol equipped with a 750 ml spacer than from an ordinary actuator should then be expected. This was found by Lindgren et al. (6), but not by later investigators.

To evaluate a new device that might give rise to a greater effect on lung function, it is mandatory to use doses that do not result in a maximum response when administered from the standard device. In dose-response studies on asthmatics with the inhalation of a bronchodilator, there seems to be a linear relationship between log dose and response in lung function with a flattening of the curve when the doses are increased (7, 12). The most striking effect of successive inhalations of terbutaline on pulmonary function was reported by Thiringer & Svedmyr (13). They administered terbutaline

by inhalation and observed a linear relationship between the dose and the response on a dose range of 0.25 mg to 4.0 mg. With excessively high doses there is a potential risk of massive administration with an ordinary actuator or a 750 ml spacer, and a small difference between the inhalation methods may be missed. For this reason we started part I of the trial with a very small amount of terbutaline and gradually increased the dose. In spite of this, the greatest response occurred after the first inhalation of only 31 µg terbutaline with a decreasing response after the subsequent inhalations, even when the doses were increased by factors of 2, 4, and 8, and no differences in pulmonary effect were found. It was surprising that such a small dose was able to induce bronchodilation at all. However, Williams et al. (16) found that 20 µg puffs of isoproterenol were as effective as the standard dose of 80 µg, and in many trials a common feature is that even large differences in doses of terbutaline are followed by the same degree of bronchodilation (4, 11).

To rule out, if possible, the question whether this large effect of 31 µg was a placebo response, part II of this study was performed.

In most asthmatics a circadian rhythm in lung function is seen, with low values in the early morning and a gradual increase during the forenoon (14). This may be the reason for the small increase in FEV₁ and FME_{25-75% corr.} 60 min after inhalation of placebo. A placebo effect might have been expected to occur immediately after the inhalation, but it was not observed. However, the inhalation of 31 µg terbutaline sulphate gave rise to a significant immediate increase in lung function that was of clinical importance. The immediate further increase after 250 µg terbutaline was not significantly greater than after the small dose.

The magnitude of lung function improvement and the pattern of decreasing response to subsequent inhalations in our trial are very similar to other cumulative dose-response trials using much larger doses (3, 5, 15). Our findings therefore confirm that the response to inhalation is influenced less by the amount of drug inhaled than by the number of times the inhalations are performed (4, 10, 11).

In spite of the plausible increase in pulmonary retention of Teflon particles demonstrated by Newman et al. (9), there was no additional effect on pulmonary function after administration of terbutaline with the 750 ml spacer. However, it cannot automatically be assumed that the hygroscopic terbutaline particles, which are likely to undergo a rapid change in the humid environment of the airways, will behave in the same manner as the non-hygroscopic Teflon particles.

The present studies suggest that the addition of a 750 ml spacer to the pressurized aerosol does not benefit patients who are able to handle an ordinary actuator. However, it has been shown that the addition of a spacer may benefit children (2).

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