

Cumulative Dose Response Study Comparing Clinical Effects of Two Doses of Terbutaline Sulphate Administered via a 750 ml Spacer to Asthmatic Patients

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Thirteen out-patients suffering from chronic reversible bronchial obstruction were treated on two separate days with two doses of terbutaline aerosol, administered with a 750 ml spacer interposed between the actuator and the mouth, in order to evaluate whether clinical responses showed a dose dependency during a 4-h period. On each day the two different doses (65 µg versus 250 µg) were inhaled three times at 15-min intervals. Fifteen minutes after the first dose there was a significant difference in FEV₁ increase between the small dose and the normal dose, FEV₁ being higher after 250 µg, but no significant differences in increase after the 2nd and 3rd inhalations. This study indicates that the bronchodilating effect of terbutaline administered via the spacer is dose-dependent at the first inhalation, and that succeeding inhalations show no dose-response effects.

Key words: asthma; dose response; spacer; terbutaline.

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Thirteen asthmatic out-patients were selected in order to study whether the initial dose of terbutaline sulphate is of any importance for the bronchodilating effect of sequential inhalation of a beta₂-agonist. The effect of a small dose (65 µg) sequentially administered three times was compared with the routine dose (250 µg) administered three times with 15-min intervals via a 750 ml spacer. In a previous study (8) we found a remarkable increase in lung function after only 32 µg terbutaline administered via a 750 ml spacer, indicating that the amount is of minor importance for the bronchodilating effect.

In this trial the patients were treated in the morning on two separate days with either a small dose or normal routine dose of terbutaline, and lung function parameters (FEV₁ and FVC) were measured during a 4-h period. At the end of the study two puffs of isoprenaline

(160 µg) were administered in order to measure further obtainable bronchodilatation.

MATERIAL AND METHODS

Patients

Thirteen out-patients (6 males and 7 females, mean age 36 years (range 22–55)) with chronic, stable and reversible asthma were included in this study. All patients used sympathomimetics, five patients, theophylline, 10, beclomethasone dipropionate aerosol, two, prednisolone and one, cromoglycate. Mean basal FEV₁ was 2.07 l (range 0.95–3.15) corresponding to 60% of expected normal value. Mean increase in FEV₁ 30 min after two puffs of isoprenaline (160 µg) was 36% (range 21–95). This spirometric test of reversibility was performed in the morning at 8.00 a.m. on a day prior to the trial.

On two consecutive days the patients attended the clinic at 8.00 a.m. and after a resting period of 15 min FEV_1 and FVC were read from spirometers obtained from a Wedge Belows spirometer "Vitalograph". (All values were corrected to BTPS values). The highest value of three measurements was used in the calculations. An individual change in starting FEV_1 values of not more than 15% between the 2 days was allowed. The patients were instructed to release one puff terbutaline into the 750 ml spacer and to empty the spacer immediately with one deep and slow inhalation from residual volume with a breath-holding pause of 10 sec or "as long as possible". At 2.5, 17.5, and 32.5 min after basal lung function was measured, terbutaline was administered in a randomized order via the spacer in doses of either 65 μ g or 250 μ g on the 2 separate days.

The aerosols were similar in appearance and the code was known only to a pharmacist, not involved in the treatment evaluation, in order to maintain the double-blind nature of the study.

FEV_1 and FVC were measured at 5, 15, 20, 30, 35, 45, 60, 90, 120, 150, 180, 210, and 240 min after basal values were obtained. At 212 min after start two puffs of isoprenaline were administered.

The patients were asked to avoid theophylline and β_2 -agonists 24 and 8 h, respectively, before the trial. Beclomethasone and cromoglycate were not allowed on trial days. The individual pretreatment spirometric value (FEV_1) on the 2 trial days was not allowed to exceed 80% of expected normal value.

Statistics

Student's t-test for paired samples was used when data were analysed, and differences were considered significant for P values of < 0.05 .

RESULTS

The mean differences between individual starting FEV_1 values on the test days was 6%. However, one patient differed more than 15%, i.e. 18%.

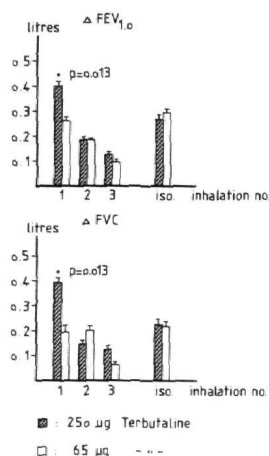


Fig. 1. FEV_1 and FVC increase in litres (mean $\pm$ SEM) after 1: 2.5 min, 2: 17.5 min, 3: 32.5 min and iso: isoprenaline inhalation.

Inhalation of 250 μ g of terbutaline compared with 65 μ g showed a significant difference ($P = 0.013$), i.e. higher mean FEV_1 and FVC values (Fig. 1).

At subsequent inhalations (2nd and 3rd) both doses produced further bronchodilatation, but no between-dose difference in bronchodilatation was observed (Fig. 1).

The 250 μ g terbutaline dose caused a significantly higher bronchodilation compared with the initial value, and produced the same FEV_1 and FVC values after the 3rd inhalation, as did the final inhalation of 160 μ g isoprenaline (Fig. 2).

This group of patients reached a mean maximal FEV_1 of 100% and FVC of 101% of the bronchodilatation produced by isoprenaline after 250 μ g administered three times at 15-min intervals (Fig. 2).

The small dose (65 μ g inhaled 3 times) produced a mean maximal bronchodilatation of 94% and 97% of the bronchodilatation produced by isoprenaline for FEV_1 and FVC, respectively. The 250 μ g terbutaline dose produced a significant increase in FEV_1 after the first inhalation 15 min after measurements were started, and this increase became highly

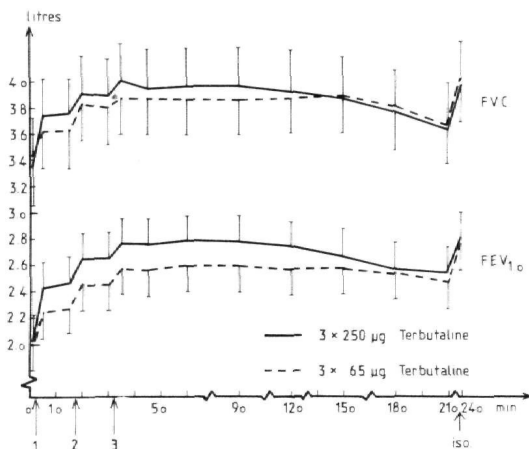


Fig. 2. FEV_1 and FVC values in litres (mean $\pm$ SEM) versus time in minutes. The terbutaline and isoprenaline inhalations are denoted with arrows.

significant ($P < 0.01$) after the 3rd inhalation and remained elevated for the succeeding 90 min. FVC showed a significant increase after the 3rd inhalation (Fig. 2).

When, however, the small dose was inhaled, no significant increase in FEV_1 and FVC was observed after the initial and succeeding doses of 65 μ g (Fig. 2).

There was no relation between individual "low" or "high" pretreatment spirometric values and effects of sequential doses.

DISCUSSION

It is well known that spacer devices interposed between the mouth and the aerosol improve the distribution of aerosol particles to the peripheral airways (1, 3, 5, 6, 8). Spontaneous variation in FEV_1 and FVC during a 4-h period is believed to be comparable on the 2 trial days, spirometric values after isoprenaline reached equal figures on the 2 days, indicating that a near maximal bronchodilatation had been reached.

Our study clearly shows that the size of the initial dose of terbutaline is of importance. A higher dose produces a better bronchodilatation than a lower (Figs. 1, 2).

The second observation of importance is the relatively equal increases in FEV_1 and FVC produced by the different succeeding doses of terbutaline. The reason for this could be that the initial activation of beta-receptors enables a better distribution of the succeeding doses (2, 4). As seen in Fig. 2, a normal dose of terbutaline (250 μ g) inhaled three times at intervals of 15 min, produced the same increased bronchodilatation as two puffs (160 μ g) of isoprenaline at the end of the observation period. In an earlier study (8) we found that sequential inhalations with intervals between doses were of importance. This has been proposed by others (2, 5, 10).

Furthermore, the small dose produced bronchodilatation of at least 4 h duration, comparable to the effect of the higher dose. However, at least some of this effect might be explained by the spontaneous variation in FEV_1 and FVC, and this could perhaps be ascertained by adding a third trial day, during which the patients received placebo.

In conclusion. The optimal initial dose of terbutaline should be 250 μ g to produce maximum bronchodilatation, followed by two doses of 250 μ g, or even 65 μ g, terbutaline at 15-min intervals in order to reach the best and most prolonged

bronchodilating effects with a minimum of such side effects as tremor and increased heart rate. It is preferable to use the 750 ml spacer interposed between aerosol and mouth to ensure that the patient receives maximal effect.

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