

Domiciliary nebulized terbutaline in severe chronic airways obstruction

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ABSTRACT: Forty-eight patients with severe chronic airways obstruction were given 5 mg terbutaline or placebo from a nebulizer twice daily for 2 + 2 weeks. Twenty three patients preferred terbutaline, 9 placebo and 16 had no preference. The baseline lung function and the 6 minute walking distance were not increased after the terbutaline period. The patients who preferred terbutaline indicated less dyspnoea after the terbutaline period as compared to the placebo period, but did not differ with regard to lung function or walking distance after the terbutaline treatment. The physiology behind the subjective relief from the terbutaline inhalations remains unexplained.

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The aim of the study was to investigate the effects of adding terbutaline from a nebulizer to the established maintenance therapy in the stable phase of chronic bronchitis with severe chronic airways obstruction.

Patients and methods

Sixty patients were included according to the following criteria: a forced expiratory volume in one second (FEV_1) <1.0 l, a history of chronic bronchitis and daily dyspnoea, and no prior treatment with a nebulizer at home. Patients with other serious diseases, obesity or a history of a decreased FEV_1 after nebulized terbutaline were not included, nor were patients receiving oxygen therapy at home. The study was in accordance with the Helsinki Declaration II, and was approved by the local Ethical Committee.

A double-blind, randomized cross-over design was used. After a 2 week run-in period with placebo inhalations the patients inhaled either 5 mg terbutaline solution (2 ml) or 2 ml placebo (isotonic saline) from a jet nebulizer (Pari Inhalierboy) twice daily for 2 + 2 weeks. Oral maintenance therapy and steroid inhalations were unchanged during the study and use of a metered dose inhaler (MDI) (0.25 mg terbutaline per dose) was allowed when needed (except for the last 4 h before visits to the chest clinic). Peak expiratory flow rate (PEF) was recorded in the home before and immediately after each treatment. At the visit after each treatment period FEV_1 and forced vital capacity (FVC) were measured on a dry spirometer before and 0, 5, 15, 30, 45, and 60 min after

inhalation of 2 ml of the nebulized drug from the period. The 6 min walking distance in a hospital corridor was measured 60 minutes after the end of inhalation.

Results

Forty-eight patients completed the study according to the protocol (24 women and 24 men). The mean age was 66 yrs (45-83 yrs). Thirty-five (73%) showed radiographic signs of emphysema - only two patients had never smoked tobacco. At the initial visit the mean FEV_1 was 0.67 l (0.36-0.96 l) or 28% of predicted (14-44%). The mean increase in FEV_1 after inhalation of 5 mg terbutaline was 19% (-2 to +68%).

Sixteen patients indicated no difference between the treatment periods regarding relief of the pulmonary symptoms, and 6 preferred the run-in period. Twenty six patients preferred one of the randomized periods: twenty three preferred the terbutaline period and 3 preferred the placebo period, $p=0.0002$, binomial test).

The median dyspnoea score on a visual analogue scale (100 mm = worst possible dyspnoea) was 47 mm (30-54 mm) after the terbutaline period, against 56 mm (38-58 mm) after the placebo period ($p=0.072$, Wilcoxon matched pairs test, 95% confidence interval of the difference: -8 to +1 mm).

Baseline lung function was not different after the terbutaline period as compared to the placebo period. FEV_1 was 0.70 l versus 0.71 l (95% confidence interval of the difference: -0.05 to +0.03 l). FVC was 1.65 l versus 1.67 l (95% confidence interval of the difference:

-0.10 to +0.06 l). The mean increases in FEV₁ were consistently higher after terbutaline inhalation compared to placebo at the visits after the randomized periods ($p < 0.01$ at all times, Wilcoxon matched pairs test). The FVC increases were similar.

The mean baseline PEF did not differ between the terbutaline and the placebo period. Morning PEF was 182 versus 179 l·min⁻¹ (95% confidence interval of the difference: -3 to +9 l·min⁻¹), evening PEF was 187 versus 183 l·min⁻¹ (95% confidence interval of the difference: -1 to +11 l·min⁻¹). The mean increase in PEF after terbutaline inhalation at home was significantly higher as compared to placebo: 11 versus 5% in the morning, 8 versus 3% in the evening, $p < 0.0001$, Wilcoxon matched pairs test).

The mean six minute walking distance was not significantly different after the treatment periods: 377 m after terbutaline and 379 m after placebo (95% confidence interval of the difference: -20 to +24 m).

The mean weight of the returned aerosol canisters was 0.36 g higher after the terbutaline period ($p = 0.046$, paired t-test). This corresponds to a reduction of 10 doses in 2 weeks (95% confidence interval: 0 to 20 doses).

The group of patients who preferred the terbutaline period had a significantly lower dyspnoea score after this period than after the placebo period (44 mm versus 56 mm, $p = 0.009$, Wilcoxon matched pairs test) in contrast to the remaining group of patients, who had the same dyspnoea score after the two treatments (50 mm versus 54 mm, ns). The mean increase in FEV₁ after terbutaline inhalation did not differ between these groups. The group who preferred terbutaline did not have a longer walking distance after this treatment compared to placebo, and was not significantly different from the remaining patients with regard to sex, age, baseline lung function, smoking habits or maintenance therapy.

Discussion

Two controlled studies have indicated a subjective relief and a reduction in simultaneous medical therapy during treatment with nebulized beta₂-agonists [1, 2] in patients with severe chronic airways obstruction. However, in these, which only comprised 9 and 8 patients respectively, the majority of the participants were using a nebulizer at home before entering the investigations. The participants in the present study had never tried domiciliary nebulizer treatment before, and the terbutaline inhalations gave subjective relief to about half of the patients. However, the baseline FEV₁, FVC and PEF did not increase during the terbutaline period and the increase in these parameters after terbutaline inhalation did not result in an increased walking distance.

The present study thus suggests that the subjective relief of dyspnoea in patients with severe chronic airways

obstruction is not associated with an increase in FEV₁ or FVC. The observed subjective relief could have been associated to an increase in small airways calibre or to a reduced resistance in the pulmonary circulation with increased left and right ventricular function as seen after intravenous or oral beta-agonist [3, 4]. Intravenous terbutaline improves the contractility of fatigued diaphragmatic muscle in the anaesthetized dog [5]. Similar effects may have a clinical importance after high dose inhalations in patients with severe chronic obstruction of the airways, but this remains to be studied.

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Terbutaline nébulisée à domicile, dans l'obstruction chronique sévère des voies aériennes. N. Hansen, O. May.

RÉSUMÉ: Quarante-huit patients atteints d'obstruction chronique sévère des voies aériennes, ont été traités par 5 mg de terbutaline ou par du placebo, au moyen d'un nébuliseur, deux fois par jour pendant 2 x 2 semaines. Vingt-trois patients ont préféré la terbutaline, neuf le placebo, et seize n'ont pas manifesté de préférence. La fonction pulmonaire de base et la distance de marche en 6 minutes n'ont pas été améliorées après la période de terbutaline. Les patients qui ont donné la préférence à la terbutaline ont signalé une dyspnée moindre après la période de terbutaline qu'après celle de placebo, mais n'ont pas été améliorés en ce qui concerne la fonction pulmonaire ou la distance de marche après le traitement à la terbutaline. L'explication physiologique du soulagement subjectif provenant des inhalations de terbutaline reste à fournir. *Eur Respir J.*, 1990, 3, 463-464.