Comparison of terbutaline and placebo from a pressurised metered dose inhaler and a dry powder inhaler in a subgroup of patients with asthma

O Selroos, A-B Låfroos, A Pietinalho, H Riska

Abstract

Background – Reversibility after administration of an inhaled bronchodilator is not always demonstrable in patients with asthma. Bronchodilator aerosol-induced bronchoconstriction has also been reported to occur in some patients.

Methods – Fifteen selected patients showing <10% improvement in forced expiratory volume in one second (FEV₁) when tested with four doses of salbutamol (0·1 mg/dose) or terbutaline (0·25 mg/dose) from a pressurised metered dose inhaler (MDI) participated in two randomised, double blind studies. They received 2·0 mg terbutaline (4 × 2 doses of 0·25 mg) or a corresponding placebo from an MDI connected to a 750 ml spacer, and 1·0 mg (2 × 0·5 mg) terbutaline or placebo from a multidose dry powder inhaler free of additives (Turbohaler).

Results – Inhalation of placebo MDI resulted in a mean (SD) decrease in FEV₁ of 20·5 (14·1)% (range – 42·9% to +2·6%). In 14 patients inhalation of 2·0 mg terbutaline MDI with spacer resulted in <10% improvement (mean increase 3·1 (6·0)%). One mg of terbutaline via a Turbohaler resulted in improvements in FEV₁ of >15% in eight patients (mean increase 16·0 (9·7)%). The improvement was <10% in four patients. Use of placebo Turbohaler did not affect airway calibre (mean change 0·2 (2·9)%).

Conclusions – Additives of MDIs may cause bronchoconstriction in some patients with asthma. In these patients inhalation from a pressurised metered dose inhaler is more likely to decrease the bronchodilator response than inhalation from an additive-free inhaler. The frequency of this phenomenon is unknown.

Thorax 1994;49:1228–1230

Most asthma patients show an improvement of at least 15% in the forced expiratory volume in one second (FEV₁) when inhaling a bronchodilator aerosol. However, although not common, acute bronchoconstriction has been observed as a complication of bronchodilator treatment with pressurised metered dose inhalers (MDIs).1,2 The causative factor is unlikely to be the active medications, but may be one of the other constituents present in the MDI.3

Irreversible airways obstruction exists when the improvement in FEV₁ is <15% (usually <10%) but where there is still – in terms of predicted values – room for an improvement of 15% or more.

Chlorofluorocarbons form an essential part of an MDI, giving the aerosol the required vapour pressure. Some studies have indicated that the chlorofluorocarbons can be bronchoconstrictive,4–6 and others have identified the lubricant – for example, oleic acid – as the bronchoconstrictive component of the MDI.7 Patients with reactive airways to bronchoconstrictor stimuli such as methacholine respond with better bronchodilatation when inhaling a β₂ agonist from a non-chlorofluorocarbon containing inhaler such as the Turbohaler than from an MDI.8 The clinical consequence of a possible sensitivity to MDI additives could be that the predicted response is reduced or absent.

This study was undertaken to investigate the true response to an inhaled β₂ agonist (terbutaline sulphate) by a selected group of patients with <10% reversibility in a standard MDI bronchodilator test.

Methods

PATIENTS

Among 82 patients participating in a screening procedure for a clinical trial we detected 17 (21%) who improved by less than 10% after inhaling four doses of salbutamol (4 × 0·1 mg) or four doses of terbutaline (4 × 0·25 mg) from an MDI. These 17 (11 women) were initially studied with respect to their bronchial reversibility in an open study with 1·0 mg terbutaline and placebo administered via an MDI with spacer and 1·0 mg terbutaline via a Turbohaler inhaler.9 The placebo MDI caused a mean (SD) decrease in FEV₁ of –16·4 (11·3)%, the terbutaline MDI a small improvement in FEV₁ (5·4 (3·4)%), and the terbutaline Turbohaler an increase of 11·0 (7·0)%. Fifteen of these 17 non-smoking patients (10 women) participated in a further two double blind studies which are reported here. Their mean age was 45·9 (13·7) years. Seven patients were atopic (skin tests, RAST, serum IgE). All had suffered from asthma for 3–7 years. Their predicted FEV₁ was 3·23 (0·53) l. Thirteen
patients were taking regular inhaled corticosteroids.

STUDY DESIGN
The patients visited the outpatient department on four days. As at the screening visit, they last inhaled a bronchodilator the preceding evening and no asthma medication was taken on the morning of the test. Oral bronchodilators had been withdrawn 48 hours earlier. They were tested at the same time each day between 08.00 and 11.00 hours. In one double blind study they received, on separate days, eight doses of placebo (2 + 2 + 2 + 2) or eight doses (2 mg) of terbutaline (2 + 2 + 2 + 2 + 2) of 0.25 mg) from an MDI attached to a spacer (Nebulhaler). The spacer loaded with two doses (placebo or 0.50 mg terbutaline) was emptied with four slow inhalations and the next two doses were thereafter immediately inserted and administered. No breath holding was applied between inhalations or after the last inhalation. In the other double blind study the patients received 1.0 mg terbutaline sulphate (two doses of 0.5 mg; one inhalation per dose) from a Turbohaler or the corresponding placebo which contained lactose. Patients were instructed to inhale with a deep and forceful inhalation technique. All four drugs were provided by Astra Draco, Lund, Sweden. As the Turbohaler delivers approximately twice as much drug to the lungs as an MDI, the doses 1.0 mg (Turbohaler) and 2.0 mg (MDI + spacer) of terbutaline were chosen to ensure that more terbutaline was not given to the patient via the Turbohaler than with the MDI.

FEV1 was measured using a Vitalograph Compact spirometer (Vitalograph Ltd, Buckingham, UK). Measurements were made before and 15 minutes after inhalation of each drug and were repeated three times. The best efforts before and after inhalation were used for the calculations. Predicted reference values were calculated according to Viljanen et al.11

All patients gave their informed consent to participate in the studies which were conducted according to GCP rules and the Declaration of Helsinki. The study protocols had been approved by the local ethics committee.

DATA ANALYSIS
Student's t tests were used for statistical comparisons of mean values, a p value of <0.05 being considered significant.

RESULTS
The results of all four reversibility tests are shown in the figure. Mean (SD) baseline FEV1 values on the study days before inhalation of study drugs were 2.42 (0.44), 2.37 (0.35), 2.39 (0.44), and 2.37 (0.43), respectively.

The test with 4 × 2 doses of placebo MDI resulted in a significant mean decrease in FEV1 of 20% (p < 0.01). A very small increase in FEV1, three a decrease of <10%, whereas 11 had a drop in FEV1 of 10% or more. With 2.0 mg terbutaline (4 × 2 doses of 0.25 mg) given via the MDI and spacer only one patient showed a >15% improvement in FEV1. The mean increase was 3.1 (6.0).%

When the patients received the bronchodilator via a Turbohaler at half the dose of terbutaline (1.0 mg), but without additives, there was a mean increase in FEV1 of 16.0 (9.7); this was statistically significant when compared with the baseline value (p < 0.05). In 11 patients FEV1 increased by 10% or more, in eight by 15% or more, and in five by 20% or more. The mean absolute increase in FEV1 with the Turbohaler was 0.36 l compared with 0.07 l with the MDI and a large volume spacer. With the placebo Turbohaler the change in FEV1 was small (0.2 (2.9) %).

DISCUSSION
The patients included in this study represented a subgroup of asthmatics who did not have a 10% improvement in FEV1 after a standard reversibility test. They were all non-smokers and most were using inhaled corticosteroids. Apart from the difference in reversibility, the patients included did not differ clinically in any other respect from the rest of the original patient population.

In recent years attention has been drawn to bronchoconstrictive properties of additives in MDIs. Acute asthmatic attacks have been reported after use of β2 agonist aerosols.12-15 Between 1984 and 1988 there were 109 cases of β agonist-induced acute bronchospasm reported to the US Food and Drug Administration.1 Acute attacks have also been reported after the use of adrenaline, isethionate, isoprenaline, orciprenaline, salbutamol, and salmeterol inhalers.

Both chlorofluorocarbons and lubricants may be bronchoconstrictive.16 Ahmad studied 10 asthma patients who used placebo inhalers containing chlorofluorocarbon 12 or a mixture of chlorofluorocarbons 11 and 12. Both aerosols caused an immediate fall in FEV1, with a mean decrease of 28% 21 minutes after inhalation.3 In another study 79 consecutively admitted asthmatic patients inhaled cumulative doses (2, 4, 8, and 16 doses) of a placebo MDI.4 A dose-response relation was found between the number of doses and the fall in FEV1. After inhalation of up to 16 doses more than half the patients had a decrease in FEV1, of
>10%, and a quarter a reduction of >20%.  
In clinical practice the possible MDI additive-induced reduction in bronchodilatation has been regarded as a minor problem. Yarbrough et al detected a fall in FEV1 of >10% in 40% of 900 patients using an orciprenaline MDI.  
In a study using a salbutamol MDI in 1450 patients bronchoconstriction occurred in 23 (1.6%). Ayres and Benincasa reported a frequency of 1.5% (180 of 11 850) of patients having a decrease of 20% or more in peak expiratory flow after administration of a salmeterol MDI.  
In order to test the hypothesis that additives of the chlorofluorocarbon inhaler could be responsible for the lack of bronchodilatation, we performed a series of tests. In an open pilot study we observed significant bronchodilatation with the additive-free inhaler (Turbohaler) but not with the chlorofluorocarbon inhaler. The pilot study was correctly criticised as not being blinded. Furthermore, later results indicated that drug deposition from the Turbohaler is about twice that from an MDI.  
In this study we have therefore tried to overcome the weaknesses in the design of the previous study. As a double blind, double dummy study was impossible, we performed two separate double blind studies. Whilst it could be argued that patients might have had a preconception of an MDI being an ineffective device, this does not explain the clear difference in response between the terbutaline MDI and placebo MDI, nor between the terbutaline Turbohaler and placebo Turbohaler.  
In order to overcome the differences in deposition between the inhalers, double the nominal dose of terbutaline was given via the MDI (2.0 mg) to ensure that the dose to the patient was at least as high with the MDI as with the Turbohaler.  
The inhalation technique had to be different in the two studies. The Turbohaler requires a deep and forceful inhalation, whereas an MDI with spacer has a very slow flow and requires less deep inhalations. The peak inspiratory flow through the inhalers was not measured, but the instructions used were identical to those when a peak inspiratory flow of 60–80 l/min was achieved through a Turbohaler and about 20 l/min through an MDI. It is therefore most unlikely that the difference between the inhalers could be explained as a result of voluntary hyperventilation during the MDI part of the study.  
The results of this study indicate that the response to terbutaline delivered via a chlorofluorocarbon-containing inhaler may be reduced in some patients with reversible airway obstruction. The frequency of this clinical problem is unknown.