

Clinical comparison of inhaled budesonide delivered either via pressurized metered dose inhaler or Turbuhaler®

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The aim of this open, randomized cross-over study was to compare the efficacy and safety of inhaled budesonide administered either via a pressurised metered dose inhaler with a 750 ml spacer attached, or via a new dry powder inhaler, Turbuhaler®, in 28 patients with stable bronchial asthma. During the 2-week run-in period, the patients received their ordinary inhaled steroid treatment. This was followed by two 4-week periods of active treatment with inhaled budesonide given via Turbuhaler or pressurized MDI. The patients were divided into two groups according to their previous, inhaled steroid doses. Group A received 400 µg of budesonide b.i.d, and Group B 800 µg of budesonide b.i.d. Diary cards were used by the patients at home to report asthma symptoms, β_2 -agonist consumption, and PEF twice daily, as well as the number of coughs experienced in a 5-min period after steroid inhalation. Budesonide Turbuhaler produced a significantly better effect on morning peak flow than budesonide MDI. The number of coughs in the 5 min after steroid inhalation was significantly lower with the Turbuhaler than with the MDI. In all other parameters recorded (e.g. FEV₁, evening PEF, histamine PC₂₀ and other diary measurements) there were no statistically significant differences between the two devices. Turbuhaler was significantly more appreciated than MDI in all questions of preference. The study showed that budesonide via Turbuhaler was at least as effective and safe as budesonide via a pressurized MDI at daily doses of 800 and 1,600 µg. The absence of additives, the lower incidence of cough after dose intake, the easiness of use, and higher preference, make Turbuhaler a valuable contribution in the treatment of asthmatics.

Key words: asthma; bronchial histamine challenge; budesonide; delivery systems; dry powder inhaler; glucocorticosteroids; topical treatment; Turbuhaler.

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Budesonide is a topically active glucocorticosteroid (GCS) used in inhalation treatment of respiratory disorders. Budesonide has been available for a number of years and is shown to be both effective and safe in the treatment of asthma (6, 8).

A new dry powder device, Turbuhaler®, has been developed for the inhalation of drug substances used in the treatment of respiratory disorders. Budesonide Turbuhaler is loaded with pure drug and so contains no additives such as propellants and lubricants. The new

inhaler system is also free of coordination problems, as it is breath-actuated. The turbulent flow of drug particles in Turbuhaler makes drug release possible even at low inspiratory flow rates (5). Thus, the new budesonide powder inhaler, Turbuhaler, differs from the conventional pressurized MDI and other dry powder delivery systems.

Previous studies in asthmatics have shown terbutaline to be equally effective when delivered either via MDI or via Turbuhaler (7, 11). However, no studies have investigated the effect

of budesonide delivered through Turbuhaler. The aim of the following study was therefore to compare the efficacy and safety of equal doses of budesonide delivered either from an MDI with a 750 ml spacer (Nebuhaler®) or from Turbuhaler.

MATERIAL AND METHODS

Design

The study was conducted as an open, randomized cross-over trial with a 2-week run-in period and two active treatment periods, each of 4 weeks duration. During the run-in period the patients continued to use their usual GCS treatment, which was in the dose range of 500–1,600 µg a day. During the two study periods, patients were stratified to treatment with budesonide in doses of either 400 µg b.i.d. (lower dose range group), or 800 µg b.i.d. (higher dose range group). A block randomization was generated by a computer stratifying patients to either the pressurized metered dose inhaler or Turbuhaler in the first treatment period. The randomization was made separately for the two dosage groups.

During the active treatment periods the patients were not allowed to change the dosage of inhaled budesonide or any other antiasthmatic medication. The inhaled budesonide was taken twice daily between 06–08 h and between 20–22 h. During both treatment periods, the patients were allowed to use inhaled β_2 -agonist on a when-needed basis; this was delivered from a pressurized MDI except for two patients using dry powder β_2 -agonist inhalers.

Prior to the run-in period, and after each treatment period, all patients underwent a bronchial histamine challenge.

Patients

The mean age was 41 years (range 19–66 years), the mean duration of asthma was 15 years. At entry into the study, the mean FEV₁ was 2.87 l (90% of predicted, range 1.61–4.36 l). Besides the inhaled steroids, all patients used

inhaled β_2 -agonists. Six patients also used oral β_2 -agonists, and 11 patients used oral theophylline. Nine patients entered the low dose group (800 µg of budesonide per day), and 20 entered the high dose group (1,600 µg of budesonide per day).

Asthma was confirmed as a 20% or greater daily fluctuation in PEF values for at least 1 week within the past 6 months, and/or bronchial reversibility test showing 15% or greater increase in FEV₁ after inhalation of 2–5 doses of a β_2 -agonist. Further, all patients should demonstrate a PC₂₀ after bronchial histamine challenge of 2 mg/ml or less. All patients used inhaled GCS in a dose between 500 and 1,600 µg daily. The dose of inhaled GCS should have been kept constant during the past 2 months. Patients were not included if pregnant or lactating, if they had experienced respiratory tract infections or a severe asthma exacerbation during the 8 weeks preceding the start of active treatment, or if they had received systemic GCS during the 8 weeks preceding the treatment. No patients were using cromoglycate, ketotifen, or short- or long-acting antihistamines. None suffered from major concomitant diseases such as, cardiac disease, reduced hepatic or renal function, or diabetes mellitus.

The study was approved by the local Ethics Committee and by the National Board of Health and Welfare. The study was conducted in accordance with the guidelines of the Declaration of Helsinki.

Lung function measurement

A lung function test was performed using a pneumotachograph with integrator (Vitalograph Compact, Vitalograph Ltd., Birmingham, U.K.). The system was calibrated before each challenge. The best of three attempts of first second forced expiratory volume (FEV₁) was chosen for statistical analysis. From this assessment, the forced vital capacity (FVC), the forced expiratory flow between 25 and 75% of vital capacity (FEF_{25–75}) and the peak expiratory flow (PEF) were recorded. The Vitalograph was slightly modified to enable the assessment of inspiratory flows and volumes through Tur-

buhaler. Three maximum inspiratory flow measurements were performed, and the peak inspiratory flow (PIF) and inspiratory vital capacity (IVC) recorded. The lung function tests were performed during each visit to the clinic. All measurements were performed at the same time of day for each patient (± 2 h). The patients were instructed not to use any inhaled β_2 -agonist in the 4 h prior to testing, if possible.

Bronchial challenge with histamine

At visits 1, 3, and 4, the patient's bronchial hyperreactivity was measured with a histamine challenge (9). All antiasthmatic medication was withdrawn prior to the test according to the European guidelines (4) except for long-acting theophyllines or long-acting oral β_2 -agonists, which were kept constant and unchanged.

After inhalation of isotonic saline, the patients inhaled increasing doses of histamine dihydrochloride generated from a Wright nebulizer (output 0.15 ml/min). Each inhalation lasted for 2 min, and FEV₁ was measured 30 and 90 s after the end of each inhalation. The next inhalation was started 5 min after the end of the previous inhalation. The test was discontinued when a 20% or greater decrease in FEV₁ compared with the post-saline value had been obtained. The concentration of histamine dihydrochloride resulting in a 20% decrease in FEV₁ was determined by linear interpolation on the log-dose response curve (PC₂₀).

Home measurements

Patients were provided with a mini Wright peak expiratory flow meter (Airmed, Clement Clarke International Ltd., London, U.K.), and instructed to record their PEF morning and evening. Patients performed three maximum expiratory manoeuvres, and the best result was recorded in the diary.

The patients also recorded their asthma symptoms (0 = none, 1 = mild (symptoms easily tolerated), 2 = moderate (some discomfort causing interference with daily life), or 3 = severe (incapacity/inability to work or do usual activity)), the daily use of β_2 -agonist

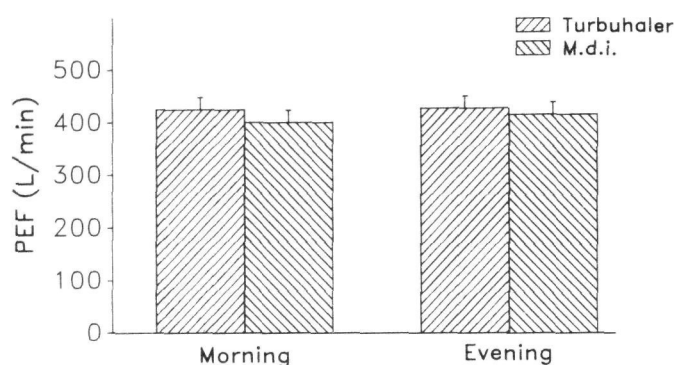


Fig. 1. Morning and evening PEF (mean $\pm$ SEM) in 28 patients treated with budesonide either via MDI or Turbuhaler.

consumption, and cough after inhalation of study drug.

Preferences

At the end of the study, the patients completed a preference questionnaire. The questions dealt with both compliance and acceptance of Turbuhaler versus MDI with Nebuhaler: General preference; ease of inhalation through the devices; size of the devices; taste; cough; hoarseness and other local irritation.

Statistics

The primary efficacy variables were FEV₁ and diary PEF (average over the last 2 weeks of each study period). Paired *t* tests were also performed on other variables from clinic visits and from patient diary cards. Wilcoxon's signed rank sum test was used to evaluate the preference questions. *P*-values < 0.05 were considered significant.

RESULTS

A total of 29 outpatients entered the study. One patient was withdrawn because of cough problems during the MDI treatment period, and 28 patients were valid for the efficacy analysis. No patients experienced any serious exacerbations during the two periods of active treatment.

There were no statistically significant differences in FEV₁ between the two treatment periods, the mean difference being 0.04 ± 0.12 (mean $\pm 95\%$ confidence interval for mean dif-

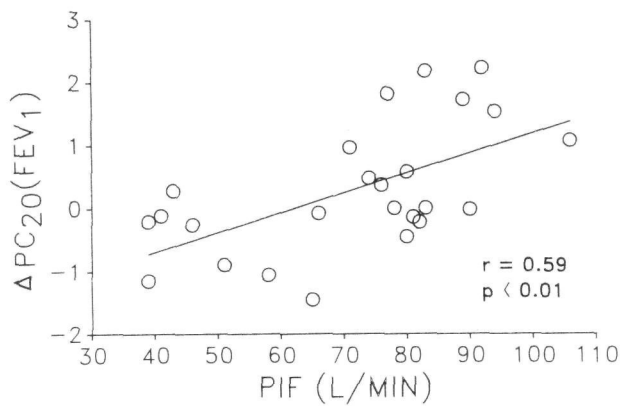


Fig. 2. Correlation between change in PC_{20} (histamine) and PIF Turbuhaler in 25 patients treated with budesonide either via MDI or Turbuhaler. x-axis: PIF through Turbuhaler (l/min) measured prior to the Turbuhaler period. y-axis: PC_{20} (histamine) expressed as the change in number of doubling concentration increases (+) or decreases (-) after the Turbuhaler period compared with the MDI period.

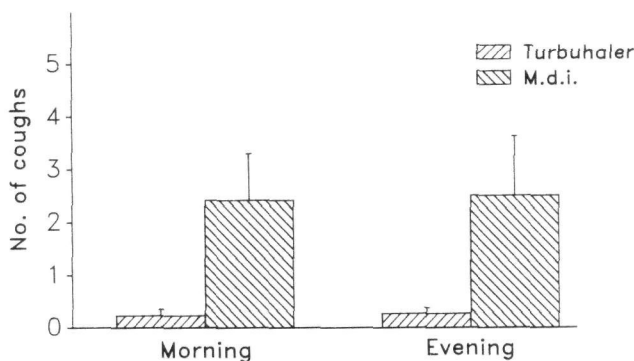


Fig. 3. Cough frequency during the 5 min after inhalation of study drug in 28 patients treated with budesonide either via MDI or Turbuhaler.

ference). Morning PEF from patients' diaries showed significantly higher values during the Turbuhaler treatment period ($P < 0.05$), but no difference in evening PEF could be demonstrated (Fig. 1).

The two treatment periods showed no statistically significant differences in FVC, FEV_{25-75} , PEF (at the clinic), and the log- PC_{20} values after bronchial histamine challenge. Peak inspiratory flow (PIF) measured through Turbuhaler was similar in the two treatment groups. No statistically significant correlation was found between PIF measured through Turbuhaler and the response measured as the difference in FEV_1 between the two treatment periods. However, the change in PC_{20} (number

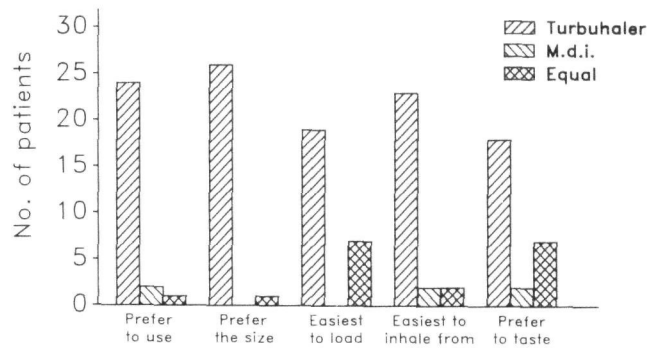


Fig. 4. Results from preference questionnaire.

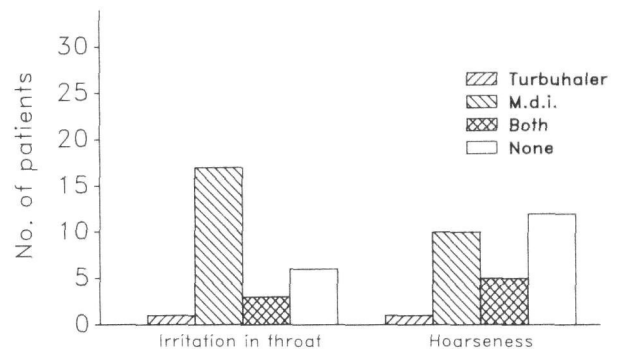


Fig. 5. Results from preference questionnaire.

of doubling concentrations) after the Turbuhaler period compared with the MDI period was significantly correlated to the peak inspiratory flow generated through Turbuhaler ($P < 0.01$; $r = 0.59$) (Fig. 2). Three patients exhibited differences in PC_{20} of between 1-2 doubling concentrations, the hyperreactivity after the Turbuhaler period being increased. All three patients had a PIF < 70 l/min through Turbuhaler. Six patients exhibited differences of between 1-3 doubling concentrations with decreased hyperreactivity after the Turbuhaler period, all showing a PIF > 70 l/min through Turbuhaler. Bronchial histamine challenge was not performed in three patients, since the FEV_1 on the test day was reduced to below 60 % of predicted. There was no significant difference in symptom scores (breathlessness, wheezing, and cough), or β_2 -agonist consumption. However, coughing after inhalation of budesonide via Turbuhaler was significantly less than after inhalation of budesonide through MDI (Fig. 3).

In all questions asked in the preference ques-

tionnaire, Turbuhaler was statistically significantly better than MDI. Nine patients with experience of other dry powder inhalers all preferred Turbuhaler (Fig. 4). No serious or unexpected side effects were noted in any treatment group. Irritation in the throat and hoarseness were more frequent during the MDI treatment period than during the Turbuhaler period (Fig. 5).

DISCUSSION

This is the first study of budesonide delivered through the new dry powder inhaler device, Turbuhaler. Previous investigations have shown that the most efficient way to use inhaled GCS in asthma is through a 750 ml spacer (10, 12). Our results show that in moderately severe asthmatics, equally dosed, budesonide through Turbuhaler is at least as efficient as MDI with a spacer. The significantly higher morning peak flow after the Turbuhaler treatment period is a sensitive marker of the current state of asthma (1), whereas we found no significant differences in the other lung function parameters or in the results of bronchial histamine challenges. There are several reasons why Turbuhaler may be more efficient than the usual MDI, even in patients trained in the use of MDI. Firstly, Turbuhaler contains pure active drug without any additives, the MDI containing fluorocarbons and lubricants in addition to the active drug. Secondly, the instructions for correct inhalation therapy are simpler with Turbuhaler than MDI, thus increasing patient compliance. Thirdly, there are no coordination problems in readying and using the Turbuhaler for inhalation.

One of the crucial points in inhaling through dry powder inhalers is the peak flow generated during the inhalation. Previous *in vitro* (5) and *in vivo* (3) investigations have demonstrated a clear correlation between the flow generated through Turbuhaler during the inhalation and the response. Most of our patients demonstrated equal, non-specific hyperreactivity as measured by bronchial histamine challenge performed after each treatment period. Some patients were unable to produce peak inspiratory flows of more than 30–40 l/min through

Turbuhaler. These patients had the same benefit from Turbuhaler treatment judging from FEV₁. However, a significant correlation between PIF through Turbuhaler and bronchial hyperreactivity was demonstrated (Fig. 2). Patients capable of producing PIF of more than 60–70 l/min through Turbuhaler may gain further benefit from inhaling budesonide through Turbuhaler.

Many patients complained of cough, discomfort and asthma symptoms after the inhalation of GCS through the MDI (2, 13). In this study we found such side effects markedly reduced when Turbuhaler was used, and Turbuhaler was preferred by most patients. As can be seen from Fig. 5, more than half of the patients complained of hoarseness related to study drug inhalation. After the Turbuhaler period only half as many had this complaint compared with the MDI period.

In conclusion, we find budesonide through Turbuhaler a valuable alternative in the treatment of asthmatics requiring topical GCS therapy. Especially patients complaining of cough, hoarseness or other discomfort from their usual inhalation therapy should be offered Turbuhaler. By completely changing the patient's therapy to dry powder inhalers, the asthma might even be substantially reduced. Further studies will have to establish the lowest PIF level at which Turbuhaler will still produce sufficient budesonide for disease control in both adults and children.

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