

A double-blind comparison between a new multi-dose powder inhaler (Turbuhaler®) and metered dose inhaler in children with asthma

C. HULTQUIST,¹ H. AHLSTRÖM,² N.-I. M. KJELLMAN,³ L.-Å. MALMQVIST,⁴
E. SVENONIUS⁵ & S. MELIN⁶

Departments of Pediatrics, ¹Lund, ²Ängelholm, ³Linköping, ⁴Kristianstad, and ⁵Malmö General Hospital, Malmö, and
⁶Dept. of Clinical Research, AB Draco*, Lund, Sweden

Turbuhaler® is a ready-loaded multiple dose inhaler which does not require co-ordination between release of dose and inhalation. 57 children with asthma participated in this clinical trial to compare the clinical effect and acceptance of terbutaline sulphate via Turbuhaler with that of metered dose inhaler (MDI). The trial consisted of two parts. In the first part of the study, which made use of a double-blind cross-over design, the clinical effect and number of treatment occasions with Turbuhaler were compared with those of MDI. In the second part, which was open, all patients were treated with Turbuhaler for 2 weeks. At the end of this period the patients were asked to make a subjective assessment of effect and to state their preference. There was no difference in clinical effect and number of treatment occasions between Turbuhaler and MDI. A majority of the patients thought Turbuhaler had the best effect and was easy to use.

Key words: beta-receptor agonists; bronchial asthma; children; terbutaline sulphate; Turbuhaler; metered dose inhaler.

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CLINICAL ASPECTS

In this study, terbutaline sulphate administered via Turbuhaler® proved to be at least as effective as terbutaline in metered doses. The children also thought the Turbuhaler was easy to use. Thus in schoolchildren, terbutaline Turbuhaler is a good alternative in the first-line symptomatic therapy of asthma.

For many years selective β_2 -agonists, such as terbutaline and salbutamol, have been first-line therapy in childhood asthma. Aerosol therapy has the advantage of rapid onset of action and few side effects. However, many children have difficulties using the metered dose inhaler (MDI) correctly (1). An alternative is the powder aerosols but these have proved inconvenient so far and in acute asthma have been difficult to use, needing high inspiratory flows (5).

Turbuhaler® is a new dry powder inhaler system which is breath-actuated. The powder contains no propellants or other additives. *In vitro*, at a flow of 60 l/min, Turbuhaler produces twice as many respirable particles (diameter $< 5 \mu\text{m}$) as the terbutaline MDI (3). The inspiratory flow needed to produce a satisfactory clinical effect can be as low as 20 l/min (6).

The present study was initiated to compare the clinical effect and acceptance of terbutaline sulphate (Bricanyl®, AB Draco, Sweden) via Turbuhaler with that of MDI in children.

* Subsidiary of AB Astra, Sweden

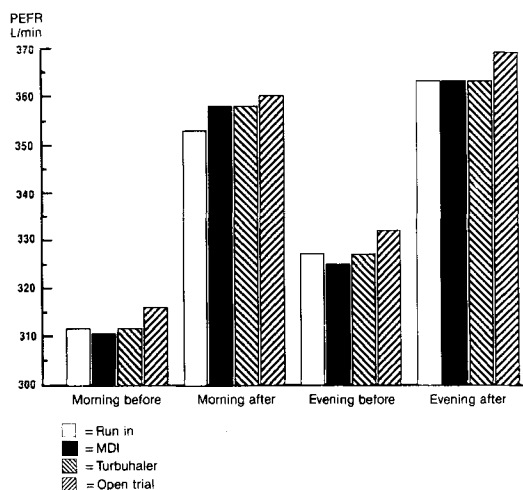


Fig. 1. PEF values morning and evening, before and after inhalation (mean).

MATERIAL

Sixty-two children with asthma, aged between 6–18 years (mean 11 years), entered the study. All had chronic reversible ($\geq 15\%$) bronchial obstruction and were well-trained in using an MDI. All treatment with oral bronchodilators, inhaled cromolyn and inhaled steroids was kept constant during the study. Children with rhinitis did not alter their treatment with nasal aerosols or oral antihistamines during the trial. No other regular treatment was allowed and no child was on oral steroids. 43 boys and 14 girls were included in the final analysis, three children having been excluded due to worsening asthma and two due to infection.

The study was of a multicenter type involving five centres. After a run-in week the study consisted of two parts. During the run-in period the children got used to their diaries, where each morning and night they entered their asthma symptom scores (score 0 = no symptoms, ..., 3 = severe symptoms), the total number of treatment occasions and the highest of the peak flow values recorded with a Mini-Wright peak flow meter before and 10 min after inhalation of β_2 -agonist. The children were asked, if possible not to use their terbutaline inhalers less than 6 h before PEF measurements.

The first part employed a double-blind, randomized, cross-over design. Using double-dummy technique the children were treated with terbutaline Turbuhaler (0.5 mg) or terbutaline MDI (2×0.25 mg) three times daily and when needed for 2 weeks each. They kept their diary cards twice daily and visited the clinic at days 1, 15 and 29. At each visit the diary cards were checked and peak flow values were recorded under observation. At the end of the 4 weeks the children stated which period they preferred.

The second part comprised a 2-week period during which the children were treated under open conditions with terbutaline Turbuhaler three times daily and when needed, but with no extra MDI. The children continued to keep diaries. When this second part was concluded, the children were asked to make a subjective assessment of the effect of the Turbuhaler and of how easy or difficult it was to use. The children were also asked if they preferred the MDI or the Turbuhaler.

In the statistical analysis of diary data, mean values over days for different periods were calculated and used as variables. For the run-in period days 3 to 5 were used in this calculation, and for the other periods days 6 to 12. When analysing the use of β_2 -inhalation the number of doses underwent logarithmic transformation before analysis. Two-way analysis of variance was performed for the measured variables followed by paired comparisons of different treatments. Preference of treatments and periods were analysed using the binomial test.

RESULTS

Of the 57 children evaluated, 53 had recorded their PEF-values as instructed. Two children had omitted to do this during the run-in period and two during the final, open period. The absolute change in l/min is given in Fig. 1. There was no change in morning and evening mean peak flow values before or after inhalation. The number of daily treatment occasions with Turbuhaler and MDI varied between 3.5 and 3.7 during the different study periods (NS). The range of the mean asthma symptom score was 0.4–0.6 during the day and 0.3–0.5 during

the night and did not vary significantly between the study periods. After the first part of the study 28 children (49%) preferred the Turbuhaler period and 13 (23%) the MDI period ($P < 0.05$), the remaining children expressing no preference.

After the second open part of the study, in which all children used active Turbuhaler, 34 (58%) of them preferred Turbuhaler, 12 (20%) preferred MDI and 13 had no preference. This difference was highly significant ($P < 0.001$). Terbutaline Turbuhaler was considered easy to use by 53 children (90%) (Fig. 2). Mild headache was the most common adverse reaction reported, 3 times after Turbuhaler and 4 times after MDI. Other complaints were occasional and mild, including nausea, tremor, tiredness, itching, rash and nose problems.

DISCUSSION

In this double-blind multicentre study we did not find any significant difference in PEF values, symptom scores or number of treatment occasions with β_2 -agonist between the two groups. Thus, terbutaline Turbuhaler proved to be as effective as terbutaline MDI in treating schoolchildren with asthma. In a cumulative dose-response study in asthmatic children Fuglsang et al. (2) obtained similar results. This is

also in agreement with results from studies comparing the effect of Turbuhaler and MDI in adults (4, 7).

Most of the children (90%) thought it was easy to learn how to use the Turbuhaler. In an open cross-over trial comparing terbutaline Turbuhaler and salbutamol (Ventolin, Glaxo) Rotacaps, Warner et al. (8) found both devices to be equally effective, although the children expressed preference for Turbuhaler as they found it easy to use. Pedersen (6) in a double-blind cross-over trial compared Bricanyl Turbuhaler and Ventoline Rotahaler in children with acute bronchoconstriction. The Turbuhaler showed significantly greater increase in FEV₁ ($P < 0.01$) and the children found it easier to operate than the Rotacaps which they were often unable to empty.

In the double-blind part of our study the children preferred the Turbuhaler period. There was also a consistent but not significant tendency towards higher PEF values with the Turbuhaler. The reason for this difference is not clear but one explanation might be the absence of Freon and other irritants in Turbuhaler. Another possible cause is the larger amount of respirable particles produced by Turbuhaler which might result in a higher terbutaline dose to the lung. This study in asthmatic schoolchildren showed terbutaline Turbuhaler to be as effective as terbutaline MDI. Because of the simpler technique needed to use the Turbuhaler accurately the children preferred it to the MDI. Thus in schoolchildren we considered terbutaline Turbuhaler to be a good alternative in the first-line symptomatic therapy of asthma.

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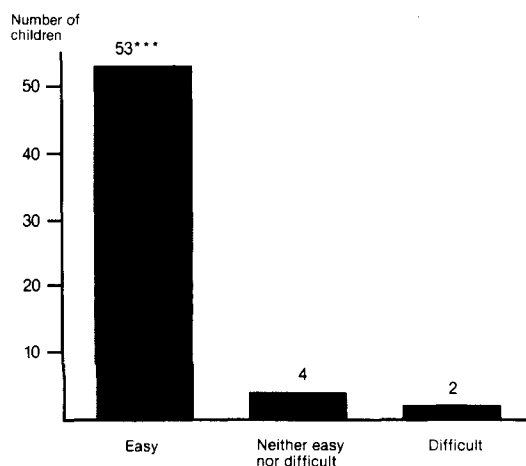


Fig. 2. Patient acceptance (Do you find Turbuhaler easy or difficult to use and handle?).

*** $P < 0.001$

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Address:
Christer Hultquist
 Dept. of Pediatrics
 University Hospital
 S-221 85 Lund
 Sweden