Salbutamol via Easyhaler® is at least as effective as salbutamol via Turbuhaler® in the treatment of histamine-induced bronchoconstriction

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The aim of this study was to compare the clinical efficacy and acceptability of salbutamol inhaled via Easyhaler® and Turbuhaler® multi-dose dry powder inhalers in the treatment of histamine-induced bronchoconstriction. Thirty-two adult patients with asthma and/or bronchial hyper-reactivity were included in the study, which was carried out according to a randomized, double-blind, double-dummy, cross-over design. Histamine challenge test was performed on 2 study days separated by at least 7 days. The challenge test was continued until a ≥20% fall in forced expiratory volume in 1 sec (FEV1) was achieved. The patients then inhaled a single 100 µg dose of salbutamol from Easyhaler®, or from Turbuhaler®. FEV1 was assessed by flow–volume spirometry before and after histamine challenge and at 1, 5, 3, 5, 10, 15, 20, 30 and 60 min after salbutamol inhalation. The primary efficacy variable was the maximum percentage change in FEV1 from the post-challenge value. The secondary efficacy variable was area under the curve (AUC) of FEV1. At the end of the study, acceptability of salbutamol Easyhaler® was evaluated using a questionnaire and Easyhaler® was also compared with the inhalation device the patient had used earlier.

Twenty-six patients completed the study. Both salbutamol Easyhaler® and salbutamol Turbuhaler® produced a rapid and significant increase in FEV1, with maximum percentage changes being 43-9% (+15-3) and 40-5% (+21-9) from the post-challenge value, respectively. There were no significant differences between the two inhalation devices in terms of changes in FEV1 or AUC of FEV1. The use of Easyhaler® and getting a new dose from Easyhaler® was considered to be very easy by 65% and easy by 35% of the patients. None considered it difficult. Of 16 patients who had used Turbuhaler® earlier, 19% considered Easyhaler® much better, 44% better, and 38% the same as Turbuhaler®, and none considered it worse.

In conclusion, the results show that salbutamol Easyhaler® was at least as effective as salbutamol Turbuhaler® in the treatment of histamine-induced bronchoconstriction. In addition, the patients considered Easyhaler® very easy or easy to use. The majority of patients who reported Turbuhaler® as their own inhaler considered Easyhaler® better or much better than Turbuhaler®.

Key words: Easyhaler®; Turbuhaler®; salbutamol; asthma; histamine-induced bronchoconstriction; hyper-reactivity.


Introduction

Salbutamol is a potent bronchodilator, acting through selective β-2 adrenergic receptor agonism. It rapidly relieves the symptoms of asthma (1) and protects against acute bronchoconstriction induced by stimuli such as exercise or inhalation of cold, dry air (2). While the use of pressurized metered dose inhalers (pMDIs) for the delivery of salbutamol has proven useful for many patients, it is associated with a number of problems. These include the potential for poor coordination between dose delivery and inhalation, and the drawbacks of CFC-containing propellants, which are both airway irritants (3) and are about to be banned due to their damaging effect on the ozone layer (4,5). Even currently available substitute propellants have some 'greenhouse gas' effects (6). Taking these factors into consideration dry powder inhalers present a better alternative for inhaled asthma therapy. They are...
breath-actuated, resolving any problems of co-ordination, and operate without the need for environmentally dam-
ing propellants.

The aim of the present study was to compare the efficacy of salbutamol delivered by the new-generation, multidose, dry powder inhaler, Easyhaler®, with that of another widely used multidose dry powder inhaler, Turbuhaler®, in histamine-induced bronchoconstriction in asthmatic and/or hyper-reactive patients.

Materials and methods

PATIENTS

Adult outpatients with documented asthma and/or hyper-reactivity were considered eligible for the study if their asthma medication had been constant for at least 4 weeks prior to the study and their forced expiratory volume in 1 sec (FEV₁) was over 65% of predicted values. Patients were also required to give written informed consent to participate in the study.

Exclusion criteria included chronic bronchitis or emphy-
sema, respiratory tract infection or vaccination with live-
attenuated influenza viruses within 4 weeks prior to the study, manifest cardiac failure (NYHA class II–IV), severe hepatic or renal disease, uncontrolled hyperthyroidism or insulin-dependent diabetes, pregnancy, inadequate contra-
ception, smoking, alcohol or drug abuse or participation in another clinical study within 4 weeks prior to this one. Patients were also excluded if they had taken beta-blockers within 4 weeks, ephedrine preparations or oral anti-
histamines within 5 days, or acrivastine within 1 day prior to study drug administration.

STUDY DESIGN

The study was carried out according to a randomized, double-blind, double-dummy, cross-over design on 2 days separated by at least 7 days (Fig. 1) in two centres in Sweden. Before each study day, patients were required to abtain from controlled-release theophylline preparations and long-acting sympathomimetics for 48 h, from inhaled anti-cholinergics and sodium cromoglycate for 12 h, and from short-acting sympathomimetics for 6 h. Patients were not allowed to drink coffee, tea, or caffeine-containing soft drinks for 4 h prior to spirometry measurements. Treat-
ments for concomitant diseases were continued unchanged during the study.

Histamine challenge tests were performed at the same time of day (± 1 h) on both study days. Before each test, FEV₁ and forced vital capacity (FVC) were measured (Vitalograph Compact Spirometer, Vitalograph Ltd, U.K.) three times and the best value was chosen. Prechallenge FEV₁ had to be more than 65% of predicted values and, on the second study day, within 15% of that recorded on the first study day. After spirometry but prior to the histamine challenge test, the patients received four breaths of isotonic saline using a jet nebulizer (Spira Elektro 2®, Spira Respiratory Care Centre Ltd, Hämeenlinna, Finland), with

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**Fig. 1. Study design.**

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the timer set to 0.5 sec and an output of 7.1 µl breath⁻¹; spirometry was then repeated.

The histamine challenge test was then started and increasing cumulative doses of histamine were inhaled. Two minutes after each dose, a single FEV₁ was measured and the challenge was continued until FEV₁ was decreased by ≥20% from the post-saline value. At this point, the histamine challenge was terminated and a 100 µg dose of salbutamol was administered either by Easyhaler® (Buvventol Easyhaler® 100 µg dose⁻¹; Orion Pharma, Espoo, Finland) or by Turbuhaler® (Inspiryl Turbuhaler® 100 µg dose⁻¹; AstraZeneca, Lund, Sweden). The correct inhalation technique was demonstrated for each device and the study drug was inhaled under the supervision of the study personnel. Spirometry was performed 1, 5, 3, 5, 10, 15, 20, 30 and 60 min after inhalation of the study drug. If a ≥20% decrease in FEV₁ was not reached at the maximum cumulative dose of histamine (2000 µg) on the first study day, the patient was withdrawn from the study.

The primary efficacy variable was the maximum percentage change in FEV₁ from the post-challenge value. The secondary efficacy variable was area under the curve (AUC) of FEV₁. Additional variables were FVC, which was measured 10, 30 and 60 min after inhalation of the study drugs, and acceptability of Easyhaler®, which was evaluated at the end of the study using a questionnaire with six questions. The questionnaire was given to the patients to fill in without help or suggestions. At the end of each study day, patients were also asked about the occurrence of any adverse events.

The study was approved by the local Ethics committees and was conducted in accordance with the Declaration of Helsinki.

STATISTICAL ANALYSIS
The study was designed to demonstrate that there was no difference between Easyhaler® and Turbuhaler® in terms of the efficacy of salbutamol inhalation. The sample size calculation was based on an assumed within-patient variation of 0.0151² for the maximum value of FEV₁. The target power of the study was 0.9 with a 5% significance level. In order to detect a difference of 0.125 between the treatments in maximum value of FEV₁ using a two-sided test, approximately 20 evaluable patients were needed.

The analysis of covariance (ANCOVA) model, including terms for patient, treatment period and sequence, was used to analyse efficacy variables. The information provided by baseline measurements was exploited through the use of covariates. Estimates of treatment difference with 95% confidence intervals was calculated. Both intention-to-treat (ITT) and per protocol (PP) approaches were used in the efficacy analyses.

Results

PATIENTS
Of the 32 patients enrolled, 26 patients completed the study. Patient demographic and baseline information is shown in Table 1. Mean prechallenge FEV₁ was the same prior to inhalation via Easyhaler® or Turbuhaler®. Thirty-eight percent of the patients were using inhaled corticosteroids, or sodium cromoglycate before and during the study.

EFFICACY
Twenty-five patients were evaluable for efficacy. Inhalation of saline had no effect on FEV₁. The mean (±sd) cumulative dose of histamine causing a ≥20% decrease in FEV₁ was 943 µg (±667) before inhalation of salbutamol from Easyhaler® and 976 µg (±981) before inhalation from Turbuhaler®. The mean decrease in FEV₁ induced by these doses was almost identical (Table 2). One patient, in the Turbuhaler® group, did not reach a ≥20% decrease in FEV₁ on the second study day at the highest cumulative dose of histamine given. In the case of this patient, a value of 4000 µg was used in the calculation of mean cumulative dose of histamine, causing a ≥20% decrease in FEV₁.

According to the ITT analysis, there were no statistically significant differences between Easyhaler® and Turbuhaler® in terms of any of the efficacy variables (Tables 2 and 3, Fig. 2). The treatment difference in maximum percentage change for FEV₁ was 1.3 percentage units with 95% CI ranging from −1.2 to 3.7 percentage units. The FVC values (Table 3) were in accordance with the FEV₁ results, reaching a maximum 30 min after salbutamol inhalation with both devices.

ACCEPTABILITY
The twenty-six patients who completed the study were included in the acceptability analysis. Both the use of

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<tr>
<td>Male/female</td>
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<td>Mean age, years (range)</td>
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<td>Mean height, cm (range)</td>
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<td>Mean weight, kg (range)</td>
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<tr>
<td>No. of atopic patients</td>
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<tr>
<td>Asthma severity (number of patients)*:</td>
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<tr>
<td>Mild</td>
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<td>Mean duration of asthma, years (range):</td>
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<td>Symptoms</td>
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<td>Mean prechallenge FEV₁, l (range):</td>
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*The severity of asthma was graded according to the International Consensus Report on Diagnosis and Treatment of Asthma (19).

n=30.
Easyhaler® and getting a new dose from Easyhaler® were considered very easy or easy by all the patients (Table 4). Inhalation from Easyhaler® was also considered to be very easy, or easy by 96% of the patients. Compared to their previous inhalers, approximately half the patients considered Easyhaler® better, or much better. Among 16 patients who used Turbuhaler® as their own inhaler, Easyhaler® was considered to be much better by 19%, better by 44%, and similar by 38%. Most of the patients felt that Easyhaler® was ‘good’ or ‘excellent’ overall, and stated that they would use Easyhaler® in the future.

TABLE 3. Mean (±sd) FVC values at baseline and 30 min after salbutamol (n = 25)

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<tr>
<th></th>
<th>Easyhaler®</th>
<th>Turbuhaler®</th>
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<tr>
<td>Baseline FVC (l)</td>
<td>3.98 (±1.00)</td>
<td>3.97 (±0.99)</td>
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<tr>
<td>Maximum FVC 30 min after salbutamol (l)</td>
<td>3.96 (±1.09)</td>
<td>3.87 (±1.03)</td>
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FIG. 2. Forced expiratory volume in 1 sec (FEV₁) before histamine challenge and after 100 μg dose of salbutamol inhaled from Easyhaler® (●) and from Turbuhaler® (○) multi-dose powder inhaler. Means ± sd, n = 25.

SAFETY

All 32 patients were included in the safety analysis. Eight patients reported AEs with Easyhaler® and four patients with Turbuhaler® after salbutamol inhalation. The number of events after Easyhaler® treatment was 15 and five after Turbuhaler®. Adverse events were mainly rated to be mild or moderate. Only two events (both headaches) were rated to be severe. Most reported events were symptoms of common cold or allergy. One patient had influenza-like symptoms on the second study day and the study was discontinued. Only in one case was the event (headache) assessed to be an adverse drug reaction (Table 5).

Discussion

Both Easyhaler® and Turbuhaler® have been shown to achieve high pulmonary deposition in the administration of β₂-agonists (7). Previous studies have also shown that delivery of salbutamol from Turbuhaler® is as effective (8) or more effective (9,10) than delivery of the same dose of
salbutamol from pMDI. Since the dose of inhaled salbutamol selected for the present study was relatively low (100 μg), and the salbutamol dose–response curve is steepest at low doses (11), this should make any possible differences in response between Easyhaler® and Turbuhaler® easily detectable. In fact, the results of the study confirmed that salbutamol delivered by Easyhaler® was at least as effective as the same dose of salbutamol delivered by Turbuhaler® at relieving histamine-induced bronchoconstriction. These data support earlier findings that the efficacy of a 100 μg dose of salbutamol via Easyhaler® dry powder inhaler is comparable to that of a 250 μg dose of terbutaline via Turbuhaler® (12) and 100 μg of salbutamol via pMDI (13).

Easyhaler® also has the advantage of being non-flow-dependent (14). This is important since one of the biggest problems in asthma therapy is incorrect use of inhalers (2). Thus, for most patients Easyhaler® appears to fulfil the definition of an ideal inhalation device: that is, it is easy to use, portable, contains multiple doses without constant refilling, requires minimal co-ordination between actuation and inhalation, and wastes little drug within the device (15).

In the present study, almost all patients considered Easyhaler® very easy or easy to use. The majority of the patients who were familiar with Turbuhaler® also preferred Easyhaler® over Turbuhaler®. These results are in accordance with the results found earlier (16).

Salbutamol inhaled from both Easyhaler® and Turbuhaler® was generally well-tolerated. Most of the adverse events reported were mild in nature and were symptoms of common cold or allergy. Many events were also of the type that was as likely to have been induced by the histamine challenge as by salbutamol dry powder inhalation. In fact, no patients reported skeletal muscle tremor, tachycardia or palpitations, which have been described previously as the main adverse events associated with salbutamol inhalation (17,18).

CONCLUSIONS

In conclusion, the results of this study show that a 100 μg dose of salbutamol via Easyhaler® is at least as effective as the same dose via Turbuhaler® after histamine-induced bronchoconstriction. All patients considered Easyhaler® easy, or very easy to use, and the majority of patients with prior experience of Turbuhaler® described Easyhaler® as better, or much better than Turbuhaler®. Salbutamol
delivery from either device was generally well-tolerated and safe.

**Acknowledgement**

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**References**