Efficacy of salbutamol via Easyhaler\textsuperscript{R} unaffected by low inspiratory flow

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The fine particle dose delivered via dry powder inhalers (DPIs) is often affected by the inspiratory flow rate generated during inhalation. This has clinical implications, since the fine particle dose determines the amount of drug reaching the lungs. With Easyhaler\textsuperscript{R} DPI the fine particle dose remains relatively constant over the range of inspiratory flow rates from 30–60 l min\textsuperscript{−1}. The aim of this study was to confirm that clinical efficacy is maintained even at low flow rates by comparing the bronchodilating effect of salbutamol (100 μg) delivered via Easyhaler\textsuperscript{R} at a target inspiratory flow of 30 l min\textsuperscript{−1} with the same dose of salbutamol via pressurised metered-dose inhaler (pMDI) plus spacer.

This was a double-blind, randomized, cross-over study with double-dummy technique. Twenty-one paediatric and adult asthmatic patients completed the study, which was conducted over 2 study days. The main outcome parameter was forced expiratory volume in 1 sec (FEV\textsubscript{1}). The patients were trained to generate a low peak inspiratory flow rate (PIFR) of 30 l min\textsuperscript{−1}, and the actual PIFR through Easyhaler\textsuperscript{R} was recorded.

The average PIFR through Easyhaler\textsuperscript{R} was 28.7 l min\textsuperscript{−1}. The difference in the maximum value of FEV\textsubscript{1} (FEV\textsubscript{1max}) between the treatments after drug inhalation was 0.01 l. The mean of FEV\textsubscript{1max} was 2.67 l after pMDI plus spacer compared to 2.69 l after Easyhaler\textsuperscript{R}. Improvements in FEV\textsubscript{1} were clinically significant. No significant differences between treatments were found.

A reasonably low inspiratory flow rate through Easyhaler\textsuperscript{R} produces an equivalent improvement in lung function to a correctly used pMDI plus spacer. Hence, Easyhaler\textsuperscript{R} can be used with confidence in patients who may have difficulty in generating a high inspiratory flow rate, such as children and the elderly.

Key words: asthma; Easyhaler\textsuperscript{R}; salbutamol; dry powder inhaler; low peak inspiratory flow; children.

Introduction

Increasingly, dry powder inhalers (DPIs) are prescribed in preference to traditional aerosols — pressurized metered-dose inhalers (pMDIs) — which are associated with a number of problems. These include sub-optimal use resulting from the failure of patients to properly coordinate inhaler actuation with inspiration (1–3), and the unacceptable environmental effects of chlorofluorocarbons (4). In addition, the propellants and lubricants in pMDIs can result in paradoxical, acute bronchoconstriction in some patients (5–9).

While DPIs can overcome the drawbacks of pMDIs, it is essential that the potential therapeutic benefit of the device can be obtained at an achievable inspiratory flow rate, since inspiratory flow rate is known to affect the amount of drug deposited in the lungs (10–14). As target inspiratory flow rate varies between different inhalers as a function of the resistance of the device, the objective of this study was to investigate the relationship between inspiratory flow rate and clinical efficacy for the new-generation DPI, Easyhaler\textsuperscript{R}.

Easyhaler\textsuperscript{R} is a multidose DPI with 200 preloaded doses. The device has been designed to resemble a pMDI (Fig. 1). However, Easyhaler\textsuperscript{R} does not require the patient to coordinate drug release and inhalation. Easyhaler\textsuperscript{R} has a dose counter showing the remaining doses in the inhaler, and uses lactose as an excipient to enable consistent drug delivery.

In an open study among asthmatic children with very low inspiratory flow rate, salbutamol inhaled via Easyhaler\textsuperscript{R} was shown to produce equivalent bronchodilatation to salbutamol via pMDI (15). Hence, the aim of this study was to confirm that the clinical efficacy of salbutamol is maintained at low flow rates through Easyhaler\textsuperscript{R}.

The bronchodilating effect of salbutamol (100 μg) via
Easyhaler® at a low flow rate (301 min⁻¹) was compared with the same dose of salbutamol via pMDI plus spacer.

Methods

SUBJECTS

Twenty-two paediatric and adult outpatients with diagnosed bronchial mild or moderate asthma were enrolled into the study (Table 1). The severity of asthma was graded according to the International Consensus Report on Diagnosis and Treatment of Asthma (16). Twenty-one patients completed the study and one was excluded due to a protocol violation. The study included both male and female patients aged from seven to 65 years. None had smoked during the 6 months prior to the study. In the 4 weeks prior to the study, all patients had shown an improvement of at least 15% in forced expiratory volume in 1 sec (FEV₁) or peak expiratory flow (PEF) following inhalation of a sympathomimetic.

The study was conducted according to the principles of the current revision of the Declaration of Helsinki of the World Medical Assembly. The independent local Ethical Committee approved the study protocol. All patients received oral and written information about the study and gave their written informed consent to participation before entering into the study.

STUDY DESIGN

The study was conducted according to a randomized, double-blind with double-dummy technique, cross-over design with a single dose regimen and two treatment periods. The study was carried out at The Skin and Allergy Hospital, HUCH, Finland. The investigational drug was 100 μg salbutamol via Easyhaler® (Buventol Easyhaler® 100 μg/dose, Orion Pharma, Finland). The comparative drug was 100 μg salbutamol via pMDI with a holding chamber (Ventolin® 100 μg/dose with Volumatic®, Glaxo Wellcome, U.K.). Placebos of both devices were also used.

The study was carried out on two study days separated by an interval of at least 24 h. The study began at the same time on both study days. The patients were randomly divided into two groups to receive salbutamol via Easyhaler® and via pMDI plus spacer. On each study day, the patients inhaled first one dose from Easyhaler® and then a dose from the pMDI plus spacer, with either of the devices being placebo. The lung function tests were measured before inhalation and three times during a 1-h period thereafter.

The investigational drug was inhaled with a low peak inspiratory flow rate (PIFR) targeted at 301 min⁻¹. Patients were taught the correct inhalation technique to achieve the target flow rate using an empty Easyhaler® in an air-tight chamber connected in series with a pneumotachograph (Spirotrack III, Vitalograph Ltd, U.K.). The drug dose from the pMDI plus spacer was inhaled within 1 sec following actuation with a low and deep inspiration according to the manufacturer’s instructions.

Before the study measurements, patients abstained from controlled-release theophylline preparations for at least 48 h, from oral and inhaled long-acting sympathomimetics, sodium cromoglycate and nedocromil sodium for at least 12 h, and from inhaled short-acting sympathomimetics for at least 6 h. The use of oral, inhaled and topical corticosteroids, and the treatment of concomitant diseases, were unchanged during the study. The patients were not allowed to drink caffeine-containing drinks for 4 h before the lung function tests.

METHODS

FEV₁, PEF and forced vital capacity (FVC) were measured with a flow volume spirometer immediately before, and 15, 30 and 60 min after inhalation of the study drug. Two exhalations with a variation in FEV₁ of less than 5% were performed and the best values were used for analysis. The difference in baseline FEV₁ values between the study days
had to be less than 15%. PIFR through Easyhaler® was measured on both study days. Adverse events (AEs) were recorded at the end of each study day as safety parameters.

ANALYSIS

The null hypothesis in this study was that the two study drug-delivery device combinations had different bronchodilating effects. The alternative hypothesis assumed equivalence of the drug-device combinations. Both primary and secondary efficacy variables were used to collect evidence against the null hypothesis. The primary determinant of therapeutic efficacy was the maximum value of FEV₁ (FEV₁\text{\text{\text{\text{\text{max}}}}}). Secondary variables included the area under the FEV₁ curve for the follow-up time, and FEV₁\text{\text{\text{\text{\text{max}}}}} as a percentage of the predicted value at baseline (during the first study day). FVC\text{\text{\text{\text{\text{max}}}}} and PEF\text{\text{\text{\text{\text{max}}}}} were treated as secondary variables.

A sample size of at least 17 patients was required to generate the statistical power necessary to detect a difference of 0–125 l in FEV₁ at the 5% significance level with 90% power. Analysis of the primary efficacy variable was performed using both Intention-To-Treat (ITT) and Per Protocol (PP) data sets. Other analyses were performed only for the ITT population. There were 17 patients in the PP data set and 21 in the ITT data set. An analysis of variance (ANOVA) model adapted for cross-over design was used for the statistical analysis of variables.

Results

PEAK INSPIRATORY FLOW RATE AND LUNG FUNCTION PARAMETERS

There was no significant difference in the primary efficacy variable between the PP and ITT data sets and, therefore, only results from ITT data set are presented. The mean (±SD) PIFR through Easyhaler® measured during the administration of active study treatment was 28·7 (±5·1) l min\(^{-1}\). The mean (±SD) of FEV₁\text{\text{\text{\text{\text{\text{max}}}}}} after the inhalation of salbutamol from Easyhaler® was increased from 2·44 to 2·69 (±0·93) l, and after inhalation from pMDI plus spacer from 2·43 to 2·67 (±0·97) l (Table 2). The estimated difference in FEV₁\text{\text{\text{\text{\text{\text{max}}}}}} between Easyhaler® and pMDI plus spacer was 0·011 (90% confidence interval from −0·07 to 0·061). Both treatment groups showed a clinically significant (>0·230) (17) improvement in FEV₁ within the first 15 min following inhalation of salbutamol. During the next 45 min there were no further significant changes (Fig. 2). The mean AUC of FEV₁ during the follow-up time was almost equal after Easyhaler® and pMDI plus spacer, 10·2 and 10·1, respectively (Table 2). The estimated difference in AUC of FEV₁ between Easyhaler® and pMDI plus spacer was 0·9 (90% confidence interval from 0·6 to 0·12).

FVC did not change significantly during the study (Table 3). In both groups, the mean of the FVC\text{\text{\text{\text{\text{\text{max}}}}}} was close to the predicted and baseline values of FVC. The PEF results paralleled the FEV₁ data (Table 3). No significant differences in primary or secondary efficacy variables were found between the treatments.

TOLERABILITY

All patients, including the one patient withdrawn after the first study day for protocol violation, were included in the safety analysis. No adverse events were reported during

| Table 2. Analyses of FEV₁ [with the exception of the AUC data, the after treatment value is the maximum value during the follow-up period. Values are means (SD)] |
|---------------------------------|-------------------------------|-------------------------------|
|                                | Easyhaler (n = 21–22)         | MDI with spacer (n = 21–22)   |
|                                | At baseline                  | After treatment               | At baseline                  | After treatment               |
| FEV₁ (l)                       | 2·44 (0·90)                  | 2·69 (0·93)                  | 2·43 (0·90)                  | 2·67 (0·97)                  |
| FEV₁ of predicted (%)          | 80·9 (10·9)                  | 89·5 (10·7)                  | 80·0 (12·3)                  | 88·0 (11·7)                  |
| AUC of FEV₁ (l min)            | —                            | 10·2 (9·1)                   | —                            | 10·1 (9·0)                   |

FIG. 2. Change in FEV₁ during the follow-up period of 60 min following inhalation of a 100 µg dose of salbutamol via Easyhaler® at low peak inspiratory flow (target 301 min\(^{-1}\)), or from pMDI plus spacer (mean ±SEM; n = 21). ▲: Easyhaler®; ●: MDI plus spacer.
the study. Both treatments with salbutamol were considered safe and without any significant adverse drug reactions following a single 100 µg dose.

DISCUSSION

In this study, the bronchodilating effect of two different types of salbutamol inhaler was compared in paediatric and adult asthmatic patients. The pMDI plus large volume spacer was used optimally according to the manufacturer's instructions. However, for this study Easyhaler® DPI was used at a lower inspiratory flow rate (targeted 301 min⁻¹) than is normally recommended. Hence, the study is likely to reflect the real situation where a patient’s ability to inhale is diminished, such as with a small child, or a person having an acute asthma attack. The lowest available dose of salbutamol via MDI and Easyhaler®, 100 µg, was used in the study trying to ensure that subjects are on a steep part of the dose–response curve instead of the plateau. However, there is a possibility that subjects would have achieved a maximal response.

There is considerable variability between DPIs in the effect of inspiratory flow rate on drug deposition and clinical efficacy. For example, with Turbuhaler® (Astra Draco, Sweden), which is one of the most widely used DPIs, the lung deposition of budesonide and terbutaline has been shown to decrease by half at low (28–361 min⁻¹) inspiratory flow compared to the optimal inspiratory flow rate of 601 min⁻¹ (10,11). Similarly, the clinical efficacy of formoterol dry powder inhaled from Aerolizer® DPI (ITALSERBER Farmaceutici Italy) is flow-dependent (12). In contrast, the clinical efficacy of another widely used DPI, Diskus® (Accuhaler®, Glaxo Wellcome, U.K.) has been reported to be almost flow-independent (18). Clickhaler® DPI (ML Laboratories PLC, U.K.) which is based on similar operating principles to Easyhaler®, has also been shown to be flow-independent in a study comparing the bronchodilating effect of 200 µg of salbutamol inhaled from Clickhaler®, and pMDI (19). However, the high dose used (200 µg) diminishes the power of the result.

The fine particle dose from the Easyhaler® is only slightly influenced by the inspiratory flow rate in vitro (20). The respirable fraction at a flow rate of 281 min⁻¹ was found to be approximately 70% of the respirable fraction created at the maximum PIFR (601 min⁻¹) through Easyhaler® (21). In a previous clinical study, Buventol Easyhaler® 200 µg dose⁻¹ produced a clear bronchodilating effect with a PIFR value as low as 161 min⁻¹ (15). It should be noted that due to high internal resistance of the Easyhaler® greater inspiratory effort is required to achieve the same inspiratory flow rate through the Easyhaler® than needed for a gentle inhalation using a MDI and a spacer. However, a sub-optimal inspiratory flow rate of about 301 min⁻¹ through the Easyhaler® is achieved very easily (15). The results of the present study with Easyhaler® are consistent with previous results showing equivalent clinical effect to a pMDI plus spacer (20,22,23). The primary equivalence criterion, FEV₁max was clearly within predefined limits.

There was no correlation between age, or PIFR and the relative treatment effect of the two devices. In the present study, even a PIFR as low as 231 min⁻¹ through Easyhaler® is sufficient to obtain a similar treatment effect to normal inhalation from a pMDI plus spacer.

Conclusions

Even a reasonably low peak inspiratory flow rate (291 min⁻¹) through Easyhaler® produces an equivalent improvement in lung function to a correctly used pMDI plus spacer. Hence, Easyhaler® can be used with confidence in patients who may have difficulties in generating high levels of inspiratory flow rate, such as children and the elderly.

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References