RESPIRATORY MEDICINE (2000) **94,** 1229–1233
doi:10.1053/rmed.2000.0959, available online at http://www.idealibrary.com on IDEAL®

Efficacy of salbutamol via Easyhaler® unaffected by low inspiratory flow

T. KOSKELA*, K. MALMSTRÖM†, U. SAIRANEN*, S. PELTOLA‡, J. KESKI-KARHU¶ AND M. SILVASTI*

*Orion Pharma, Easyhaler Project, Kuopio, †Helsinki University Central Hospital, Hospital for Children and Adolescents, Helsinki, ‡University of Kuopio, Kuopio and ¶Orion Pharma, Dept. of Biostatistics, Kuopio, Finland

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® DPI the fine particle dose remains relatively constant over the range of inspiratory flow rates from 30–60 l min^{-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® at a target inspiratory flow of 30 l min^{-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_1). The patients were trained to generate a low peak inspiratory flow rate (PIFR) of 30 l min^{-1}, and the actual PIFR through Easyhaler® was recorded.

The average PIFR through Easyhaler® was 28·7 l min^{-1}. The difference in the maximum value of FEV_1 (FEV_{1max}) between the treatments after drug inhalation was 0·01 l. The mean of FEV_{1max} was 2·67 l after pMDI plus spacer compared to 2·69 l after Easyhaler®. Improvements in FEV_1 were clinically significant. No significant differences between treatments were found.

A reasonably low inspiratory flow rate 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 difficulty in generating a high inspiratory flow rate, such as children and the elderly.

Key words: asthma; Easyhaler®; salbutamol; dry powder inhaler; low peak inspiratory flow; children.

RESPIR. MED. (2000) **94**, 1229–1233

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 co-ordinate 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®.

Easyhaler® is a multidose DPI with 200 preloaded doses. The device has been designed to resemble a pMDI (Fig. 1). However, Easyhaler® does not require the patient to co-ordinate drug release and inhalation. Easyhaler® 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® 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®. The bronchodilating effect of salbutamol (100 μg) via

Received 29 June 2000 and accepted in revised form 24 August 2000.
Correspondence should be addressed to T. Koskela, Orion Corporation, Orion Pharma, Volttikatu 8, P.O. Box 1780, FIN-70701, Kuopio, Finland. Email: tommi.koskela@orionpharma.com; Fax: +358 17 245 444.

0954-6111/00/121229+05 $35·00/0

FIG. 1. Easyhaler® multidose powder inhaler.

Easyhaler® at a low flow rate (30 l 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 (FEV_1) 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.

TABLE 1. Demographics and baseline features at the beginning of the study ($n = 22$)

Gender (male/female)	10/12
Age (years)	19 (7–65)*
— number of patients under 16 years	12
Height (cm)	155 (120–183)*
Weight (kg)	51 (20–96)*
Number of atopic subjects	17
Severity of asthma (mild/ moderate)	7/15
Duration of asthma symptoms (years)	5.6 (6.8)†
Duration of asthma (years since diagnosis)	5.1 (7.2)†

Values are means ± range* or SD† (range or SD shown in parentheses), except in relation to sex, number of atopic subjects or severity of asthma.

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 30 l 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

FEV_1, 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 FEV_1 of less than 5% were performed and the best values were used for analysis. The difference in baseline FEV_1 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 FEV_1 (FEV_{1max}). Secondary variables included the area under the FEV_1 curve for the follow-up time, and FEV_{1max} as a percentage of the predicted value at baseline (during the first study day). FVC_{max} and PEF_{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 FEV_1 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 FEV_{1max} 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 FEV_{1max} between Easyhaler® and pMDI plus spacer was 0·01 l (90% confidence interval from −0·07 to 0·06 l). Both treatment groups showed a clinically significant (>0·230 l) (17) improvement in FEV_1 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 FEV_1 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 FEV_1 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_{max} was close to the predicted and baseline values of FVC. The PEF results paralleled the FEV_1 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

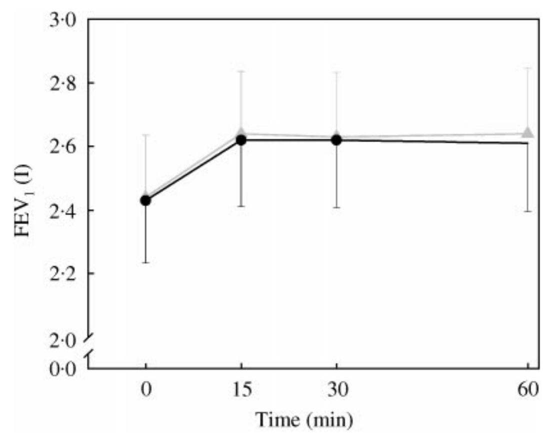

FIG. 2. Change in FEV_1 during the follow-up period of 60 min following inhalation of a 100 μg dose of salbutamol via Easyhaler® at low peak inspiratory flow (target 30 l min^{-1}), or from pMDI plus spacer (mean ± SEM; $n = 21$). ▲: Easyhaler®; -●-: MDI plus spacer.

TABLE 2. Analyses of FEV_1 [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
FEV_1 (l)	2·44 (0·90)	2·69 (0·93)	2·43 (0·90)	2·67 (0·97)
FEV_1 of predicted (%)	80·9 (10·9)	89·5 (10·7)	80·0 (12·3)	88·0 (11·7)
AUC of FEV_1 (l min)	—	10·2 (9·1)	—	10·1 (9·0)

TABLE 3. Analyses of PEF and FVC [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
FVC (l)	3·26 (1·17)	3·35 (1·19)	3·25 (1·17)	3·31 (1·18)
FVC of predicted (%)	97·0 (10·3)	99·9 (10·1)	96·7 (10·4)	98·5 (10·8)
AUC of FVC (l min)	—	0·9 (7·0)	—	−0·8 (6·6)
PEF (l min^{-1})	300 (123)	337 (142)	295 (124)	338 (142)
PEF of predicted (%)	71·4 (12·5)	79·7 (14·6)	69·9 (14·9)	79·8 (14·9)
AUC of PEF (l min)	—	1462 (1523)	—	1591 (1510)

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 30 l 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 (28–36 l min^{-1}) inspiratory flow compared to the optimal inspiratory flow rate of 60 l min^{-1} (10,11). Similarly, the clinical efficacy of formoterol dry powder inhaled from Aerolizer® DPI (ITALSEBER 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 28 l min^{-1} was found to be approximately 70% of the respirable fraction created at the maximum PIFR (60 l 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 16 l 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 30 l 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, FEV_{1max} 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 23 l 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 (29 l 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.

Acknowledgements

The authors thank the participated investigators Timo Helin, MD and Liisa Raatikainen, MD, from Helsinki University Central Hospital, Hospital for Children and Adolescents, Helsinki, Finland, and Ritva Sorva, MD and Kaisu Juntunen-Backman, MD, for their contribution to the study protocol. Special thanks goes to the study nurses Merja Helske, Pirkko Leskelä and Raila Pitkänen.

References

1. Crompton GK. Problems patients have using pressurized aerosol inhalers. *Eur J Respir Dis* 1982; **63** (Suppl.119): 101–104.
2. Epstain SW, Manning CPR, Ashley MJ, Corey PN. Survey of the clinical use of pressurized aerosol inhalers. *Can Med Assoc J* 1979; **120:** 813–816.
3. Shim Ch, Williams MH. The adequacy of inhalation of aerosol from canister nebulizers. *Am J Med* 1980; **69:** 891–894.
4. The Commission of the European Countries: Commission Decision of 26 July 1995 on the quantities of controlled substances allowed for essential uses in the Community in 1996 under Council Regulation (EC) No 3093/94 on substances that deplete the ozone layer (95/324/BC). Brussels, EC, 1995.
5. Nicklas RA. Paradoxical bronchospasm associated with the use of inhaled beta agonists. *J Allergy Clin Immunol* 1990; **85:** 959–964.
6. Cocchetto DM, Sykes RS, Spector S. Paradoxical bronchospasm after use of inhalation aerosols: a review of the literature. *J Asthma* 1991; **28:** 49–53.
7. Wilkinson JRW, Roberts JA, Bradding P, Holgate ST, Howarth PH. Paradoxical bronchoconstriction in asthmatic patients after salmeterol by metered dose inhaler. *Br Med J* 1992; **305:** 931–932.
8. Yarborough J, Mansfield LE, Ting S. Metered dose inhaler induced bronchospasm in asthmatic patients. *Ann Allergy* 1985; **55:** 25–27.
9. Sterling GM, Batten JC. Effect of aerosol propellants and surfactants on airway resistance. *Thorax* 1969; **24:** 228–231.
10. Newman SP, Moren F. Trofast E, Talaee N, Clarke SW. Terbutaline sulphate Turbuhaler: effect of inhaled flow rate on drug deposition and efficacy. *Int J Pharm* 1991; **74:** 209–213.
11. Borgström L, Bondesson E, Moren F, Trofast E, Newman SP. Lung deposoition of budesonide inhaled via Turbuhaler®: a comparison with terbutaline sulphate in normal subjects. *Eur Respir J* 1994; **7:** 69–73.
12. Nielsen KG, Skov M, Klug B, Ifversen M, Bisgaard H. Flow-dependent effect of formoterol dry-powder inhaled from the Aerolizer®. *Eur Respir J* 1997; **10:** 2105–2109.
13. Richards R, Simpson SF, Renwick AG, Holgate ST. Inhalation rate of sodium cromoglycate determines plasma pharmacokinetics and protection against AP-induced bronchoconstriction in asthma. *Eur Respir J* 1988; **1:** 896–901.
14. Olsson B, Asking L. Critical aspects of the function of inspiratory flow driven inhalers. *J Aerosol Med* 1994; **7** (Suppl. 1): 43–47.
15. Malmström K, Sorva R, Silvasti M. Application and efficacy of the multidose powder inhaler, Easyhaler®, in children with asthma. *Pediatr Allergy Immunol* 1999; **10:** 66–70.
16. National Heart, Lung, and Blood Institute, National Institute of Health. International consensus report on diagnosis and treatment of asthma. *Eur Respir J* 1992; **5:** 601–641.
17. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial. *Eur Respir J* 1999; **14:** 23–27.
18. Nielsen KG, Auk IL, Bojsen K, Ifversen M, Klug B, Bisgaard H. Clinical effect of Diskus™ dry-powder inhaler at low and high inspiratory flow-rates in asthmatic children. *Eur Resp J* 1998; **11:** 350–354.
19. Newhouse MT, Nantel NP, Chambers CB, Pratt B, Parry-Billings M. Clickhaler (a novel dry powder inhaler) provides similar bronchodilation to pressurized metered-dose inhaler, even at low flow rates. *Chest* 1999; **115:** 952–956.
20. Palander A, Halme A, Kananen M, *et al. In vitro* performance of inhalers: salbutamol containing dry powder products. *J Aerosol Med* 1999; **12:** 113.
21. Vidgren M, Silvasti M, Vidgren P, Sormunen H, Laurikainen K, Korhonen P. Easyhaler® multiple dose powder inhaler — Practical and effective alternative to the pressurized MDI. *Aerosol Sci Technol* 1995; **22:** 335–345.
22. Vidgren M, Silvasti M, Korhonen P, Kinkelin A, Frischer B, Stern K. Clinical equivalence of a novel multiple dose powder inhaler versus a conventional metered dose inhaler on bronchodilating effects of salbutamol. *Arzneim.-Forsch./Drug Res.* 1995; **45:** 44–47.
23. Haahtela T, Vidgren M, Nyberg A, Korhonen P, Laurikainen K, Silvasti M. A novel multiple dose powder inhaler. Salbutamol powder and aerosol give equal bronchodilatation with equal doses. *Ann Allergy* 1994; **72:** 178–182.