Assessment of patient performance of the HandiHaler® compared with the metered dose inhaler four weeks after instruction

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Summary

The HandiHaler® is a novel breath-actuated dry powder system designed for the delivery of tiotropium 18 μg daily in the treatment of COPD. We compared patient ability to use the HandiHaler® or metered dose inhaler (MDI) device correctly 4 weeks after receiving brief instructions and device demonstration. A single-blind study was conducted in COPD patients in two centers in Denmark. All patients (n = 151) received one placebo capsule via the HandiHaler® daily and ipratropium (20 μg) two actuations via the MDI q.i.d. Mean FEV₁ for all patients was 1.25 ± 0.54 (46% predicted). Twelve instructions establishing proper device use were evaluated for the MDI and Handihaler. Error scores were analyzed by number of patients with less, equal or more errors when using HandiHaler® compared to MDI in the total efficacy population (n = 139) and according to those who had not previously used an MDI for at least 12 months (MDI beginners) (n = 74) and those who had used an MDI (MDI experienced) (n = 65). Four weeks after device instruction, a higher proportion of patients in the total population (P < 0.01) had fewer errors with the HandiHaler® (35.3%) compared to the MDI (15.1%). The number of errors was equal in 50% of patients. Similar findings were observed in the subgroup of patients who were MDI beginners (42% vs. 11%, P < 0.01) with non-significant trends in favor of the HandiHaler® in those patients who were MDI experienced (29.7% vs. 18.9%, P = 0.096). Similar results in favor of HandiHaler® were noted across different age and sex strata. The proportion of patients correctly using the device on the first of three attempts was 59.7% and 54.7% for the HandiHaler® and MDI, respectively (P = 0.399). In summary, use of the HandiHaler® can be easily taught with fewer errors compared to the MDI. Furthermore, patient performance using the HandiHaler® was superior to that with an MDI despite prior MDI experience and more frequent usage.

Introduction

Inhaled bronchodilators have been a mainstay for drug delivery in chronic obstructive pulmonary disease (COPD) for many years. Several devices have been developed to administer inhaled
pharmacotherapy. There are currently three main categories of inhaled medication delivery devices. These include: (1) pressurized metered dose inhaler (MDI), (2) dry powder inhalation systems (DPI) and (3) liquid nebulization systems. The MDI and DPI systems are the most common prescribed and used delivery devices while the nebulizers are generally reserved for use in the hospital setting. The HandiHaler® is a dry powder inhaler system developed for the delivery of tiotropium (SPIRIVA®) to COPD patients. Operation of the HandiHaler® is based on the evacuation of powder medication from a pierced capsule that is achieved by an inspiratory maneuver by the patient. Studies using the Andersen Cascade Impactor have shown that 20 l/min is an effective inspiratory flow rate to cause evacuation of powder from the capsule containing the medication. Additional studies in COPD patients with low FEV1 (16–65% predicted) have confirmed that the HandiHaler® can be used effectively. Long-term multi-center studies with tiotropium have confirmed that an effective dose resulting in bronchodilation and improved symptomatic control can be delivered with the HandiHaler® dry powder inhalation system. Given that the most common option used for delivery of inhaled medication is the MDI, a trial was conducted to determine whether use of the HandiHaler® was associated with less performance errors compared to the MDI and to assess the ability of COPD patients to learn how to use the HandiHaler®.

Methods

Study design

This was a 4-week, single-blind trial in COPD patients to compare the HandiHaler® to a pressurized MDI with regards to self-administration technique and the retention of the learned ability to correctly self-administer medication through each device. The patients were instructed, trained, and assessed on use of HandiHaler and MDI. Patients self-administered placebo capsules (lactose) once daily with the HandiHaler® and ipratropium bromide via the MDI two actuations q.i.d. The patients but not the investigators were blinded to the treatment.

Patients

All patients were required to have a diagnosis of COPD according to American Thoracic Society Criteria and have documented airflow limitation with an FEV1 ≤80% of predicted normal and FEV1 ≤70% of FVC. Spirometry conducted up to 6 months prior to the first visit was accepted. Patients were to be at least 40 years of age and have had a history of smoking of more than 10 pack-years. All patients were required to have been using an inhaled bronchodilator at least once daily. Patients were excluded if, in the opinion of the investigator, they had any acute or chronic illness that could interfere with the conduct or completion of the trial, had previously used the HandiHaler® or discontinued use of regularly prescribed MDI within the last 12 months. Patients who had a recent (within 6 weeks prior to Visit 1) respiratory illness or had participated in a pulmonary rehabilitation program in the 6 weeks prior to Visit 1 were also excluded. The protocol was approved by the local scientific ethics committee in Aarhus and Copenhagen, and written informed consent was obtained before any study procedure was undertaken.

There were two populations of 80 patients planned each serving as stratification groups. The first population consisted of those patients who were using an MDI at the time of study enrolment (MDI experienced). The second population (MDI beginners) consisted of those patients who had not used an MDI in the preceding 12 months. Patients were recruited from two centers in Denmark. Each center was expected to randomize 80 patients. Patients were recruited from out patient clinics at the two hospitals and through advertising in local newspapers.

Study protocol

The trial consisted of two visits separated by 4 weeks. At Visit 1, patients were instructed and trained in correct use of both the HandiHaler® and the MDI. Thereafter, all patients were asked to demonstrate that they were able to follow the instructions by a 12-step checklist assessment for each device (Table 1). Placebo MDI and placebo capsules were used at Visits 1 and 2 when demonstrating and observing the patient’s administration technique of both devices. Only patients who were not able to demonstrate use of the devices without errors after the third attempt were included in the trial by the investigator. At Visit 1, prescribed inhaled anticholinergics, regularly scheduled short-acting β-agonists and combination (anticholinergic and β-agonists) products were discontinued. The patients took the last dose of these medications on the morning of Visit 1.
Patients who were eligible for the trial were provided with one blinded MDI containing ipratropium bromide, to be taken at a dose of two puffs four times daily, starting in the morning after Visit 1. Patients were also provided with a HandiHaler® device and blinded placebo capsules to be taken at a dose of one capsule, once daily, starting in the morning after Visit 1. The patients were provided with an open-label salbutamol MDI labeled as rescue medication. The patients were informed that they would receive a bronchodilator but were not informed which device contained active drug. The patients were sent home with the HandiHaler® device, placebo capsules, a blinded ipratropium MDI and a labeled salbutamol MDI for 4 weeks. At Visit 2, which occurred after 4 weeks, the patients took the last dose of study medication on the morning of Visit 2 before meeting at the outpatient clinic. At Visit 2 investigators repeated the assessment of both devices in randomized sequence (Table 2).

Data analysis

The differences in error rates were tested by means of a two-sided Wilcoxon signed rank test at level of significance of 0.05, using the individual differences in the number of errors when using the two devices. In addition, the error rates were also analyzed by means of a linear model including factors for device, sequence, patient within sequence, period, center and population. Main effects and possible interactions were explored. The number of errors made on all scoring attempts at Visit 1 were compared between the devices using the same method as that for the primary endpoint. The number of scoring attempts at Visit 1 were evaluated by frequency tables and the McNemar test (post hoc analysis) and compared between the devices.

Results

A total of 152 patients were randomized. One hundred and fifty-one patients were treated, 81 in the group of MDI beginners and 70 in the group with MDI experience. Sixteen patients (10.6% out of 151 randomized and treated patients) discontinued the study prematurely (11 MDI beginners and five with MDI experience), and 135 patients completed the study (70 MDI beginners and 65 with MDI experience). However, data from Visit 2, available on four discontinued patients (all were MDI beginners), were included in the analysis. No differences were demonstrated between the two centers. Center 1 randomized and treated 72 evaluable patients and
center 2 randomized and treated 79 evaluable patients.

Patient demographics

A total of 93 men (61.6%) participated in the trial. The mean age was $67 \pm 8$ years with a mean FEV$_1$ of $1.25 \pm 0.54$ l (46 $\pm$ 16% predicted). Nearly all patients (147/151) were receiving pulmonary medication at baseline.

Performance scores

Prior to instructions and demonstration regarding their use of the MDI, MDI experienced patients were rated according to the 12-step performance checklist at Visit 1. Fifty-four patients out of 70 (77.1%) of the population with MDI experience were unable to use the MDI device without error (Fig. 1). At Visit 1, patients needed to demonstrate correct use of both devices after instruction and demonstration of the use of both devices to remain in the study after randomization. A maximum of three attempts was allowed. In the total efficacy population, 59.7% (HandiHaler$^R$) and 54.7% (MDI) ($P = 0.399$) of patients recorded proper use on the first attempt and all patients demonstrated correct use within three attempts (Fig. 2). In the group of MDI beginners (74 patients of the efficacy population) there were more patients who succeeded with their first demonstration of HandiHaler$^R$ use (58.1%) vs. MDI use (40.5%) ($P = 0.037$), and more patients needed two or three attempts for successful use of MDI than for HandiHaler$^R$ (Fig. 2). As would be expected, the reverse was found for the group of MDI experienced patients (65 patients of the efficacy population). There were more patients successful with their first demonstration in MDI use (70.8%) vs. HandiHaler$^R$ use (61.5%) and more patients needed two or three attempts for successful use of HandiHaler$^R$ than for MDI.

The group of MDI beginners demonstrated more errors with use of the MDI than with the HandiHaler$^R$. Thirty-one patients (41.9%) made more errors using MDI than using HandiHaler$^R$, and 21 patients (28.4%) made more errors using HandiHaler$^R$ than using MDI. These observed differences between the use of the MDI and the HandiHaler$^R$ among beginners were without statistical significance. The mean for the difference of error rates was $-0.27$ (HandiHaler$^R$–MDI) and was statistically significant different from zero ($P < 0.05$). The group of MDI experienced patients demonstrated more errors with the HandiHaler$^R$ than with the MDI. The mean for the difference of error rates was $+0.17$.

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**Table 2**  Patient characteristics at screening.

<table>
<thead>
<tr>
<th></th>
<th>Total patients (N = 151)</th>
<th>MDI-beginner (N = 81)</th>
<th>MDI-experienced (N = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>62</td>
<td>62</td>
<td>61</td>
</tr>
<tr>
<td>Age (years)$^a$</td>
<td>67.1 (7.9)</td>
<td>66.2 (8.3)</td>
<td>68.0 (7.4)</td>
</tr>
<tr>
<td>Duration of COPD (years)$^a$</td>
<td>10.4 (7.6)</td>
<td>9.6 (7.1)</td>
<td>11.3 (8.1)</td>
</tr>
<tr>
<td>Smoking history (pack-years)$^a$</td>
<td>36.4 (16.3)</td>
<td>33.6 (15.1)</td>
<td>39.6 (17.1)</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>55.0</td>
<td>55.6</td>
<td>54.3</td>
</tr>
<tr>
<td>Baseline medications (% population)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any pulmonary medication</td>
<td>97</td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>Inhaled salbutamol</td>
<td>38</td>
<td>20</td>
<td>59</td>
</tr>
<tr>
<td>Inhaled salmeterol</td>
<td>40</td>
<td>42</td>
<td>39</td>
</tr>
<tr>
<td>Inhaled anticholinergic</td>
<td>33</td>
<td>26</td>
<td>40</td>
</tr>
<tr>
<td>Inhaled steroid</td>
<td>45</td>
<td>49</td>
<td>40</td>
</tr>
</tbody>
</table>

$^a$Mean (SD).
(HandiHaler®-MDI) but was not statistically significantly different from zero.

After 4 weeks use at Visit 2, the patient performance of device use was rated (Table 3). More patients had at least one error with the MDI compared with the HandiHaler® (56.8% out of 139 patients of the efficacy population with errors in MDI use and 46.0% with errors in HandiHaler® use). This result was also observed in the subgroups defined by MDI experience. Twenty-one patients (15.1%) made more errors using the HandiHaler® than using MDI and 49 patients (35.3%) made more errors using the MDI than using HandiHaler®. This observed difference between results for devices was statistically significant (P<0.01). In addition, the observed difference between results for devices was statistically significant (P<0.01) when patients were stratified according to MDI experience. The difference in the subgroup of MDI beginners was numerically but not statistically different in favor of the HandiHaler® (P = 0.096).

Due to inconsistent interpretation of one specific patient instruction for the devices across centers, the primary analysis was repeated ignoring step 10 of the HandiHaler® performance checklist ('Remove the HandiHaler® out of the mouth and breath out slowly') and step 9 of the MDI performance checklist ('Remove the inhaler from the mouth and breathe out'). The judgement of what constituted 'breathing out slowly' was different between centers. As this does not impact delivery of medication, the analysis excluding this step was relevant. The results of the primary analysis were confirmed. Furthermore, patients made statistically significantly fewer errors using HandiHaler® than using MDI within all analyzed subgroups using both, Wilcoxon signed rank test (P<0.0133) and ANOVA (Table 4).

### Age and gender analysis

The performance results following 4 weeks of use (Visit 2) were categorized according to the age and gender of the patients. For both devices, the incidence of errors increased with age; however, in all age subgroups, the percentages of patients correctly performing every step of HandiHaler® use

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**Table 3** Number of patients with errors for performance checklists at Visit 2.

<table>
<thead>
<tr>
<th></th>
<th>HandiHaler®</th>
<th>MDI device</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>MDI-beginner</td>
</tr>
<tr>
<td>Patients, n (%)</td>
<td>139 (100)</td>
<td>74 (100)</td>
</tr>
<tr>
<td>Patients with ≥1 error, n (%)</td>
<td>64 (46.0)</td>
<td>32 (43.2)</td>
</tr>
<tr>
<td>Errors per patient, mean (SD)</td>
<td>0.7 (0.9)</td>
<td>0.7 (0.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>MDI device</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
</tbody>
</table>

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**Table 4** Number of patients with errors for performance checklists at Visit 2 excluding step 10 for the HandiHaler® and step 9 for the MDI.

<table>
<thead>
<tr>
<th></th>
<th>HandiHaler®</th>
<th>MDI device</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>MDI-beginner</td>
</tr>
<tr>
<td>Patients, n (%)</td>
<td>139 (100)</td>
<td>74 (100)</td>
</tr>
<tr>
<td>Patients with ≥1 error, n (%)</td>
<td>33 (23.7)</td>
<td>15 (20.3)</td>
</tr>
<tr>
<td>Errors per patient, mean (SD)</td>
<td>0.3 (0.7)</td>
<td>0.3 (0.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>MDI device</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
</tbody>
</table>

were higher than for MDI use (Fig. 3). The incidence of errors occurring while demonstrating the use of either device at Visit 2 was higher in female patients than in male patients. For both sexes, a greater percentage of patients correctly demonstrated use of the HandiHaler\textsuperscript{K} compared with correct use of the MDI (Fig. 4).

Discussion

Inhaled therapies are the preferred treatment modalities for COPD.\textsuperscript{1} Assuring the proper training of health care professionals, correct patient use of inhaled delivery systems and improved compliance continues to be a challenge in meeting treatment goals for COPD. To complicate this matter, the ideal delivery device needs to be designed with considerations for providing consistent delivery of a set amount of medication of the optimal particle size, to the lung. In this report we have compared the self-administration performance using either the HandiHaler\textsuperscript{K} or MDI over the course of a 4-week clinical trial in COPD patients.

The HandiHaler\textsuperscript{K} is a breath activated dry powder system for delivery of tiotropium 18\textmu g, once daily. As the MDI remains the most common mode of delivering inhaled medication world-wide, a comparison of the ability to learn how to use the HandiHaler\textsuperscript{K} and MDI and retention of such learning was performed.\textsuperscript{8} Initial instruction was followed by an uninterrupted 4-week period of use. To replicate the actual frequency of use over the course of a day, patients were instructed to use the HandiHaler\textsuperscript{K} once daily and use the MDI four times daily. At the end of 4 weeks, the HandiHaler\textsuperscript{K} appeared easier to learn, by virtue of fewer mistakes associated with use, compared to the MDI, and this difference was statistically significant. After instruction and demonstration, MDI inexperienced patients needed fewer attempts to demonstrate appropriate HandiHaler\textsuperscript{K} use than did patients using the MDI. After 4 weeks, MDI beginners as well as MDI experienced patients made fewer errors using the HandiHaler\textsuperscript{K} than MDI. In addition, a lower proportion of patients had one or more errors using the HandiHaler\textsuperscript{K} vs. the MDI, although this did not reach statistical significance. Patients using the HandiHaler\textsuperscript{K} delivery device made fewer errors compared with those who used the MDI and were better able to retain instructions for proper use.

Bronchodilator therapy for the treatment of COPD may be administered by oral, sub-cutaneous, intravenous or inhaled route for drugs with topical activity. Inhalation provides the therapeutic advantage of local delivery to the lung, thereby, reducing the required dose for bronchodilation and minimizing the potential for adverse effects by systemic bioavailability. Inhalation of bronchodilators also allows for a more rapid onset of action compared with systemic delivery.\textsuperscript{9} DPI systems have been widely used and have gained acceptance over the last decade and have several advantages over pressurized aerosol systems. DPIs do not contain propellants and are therefore, in compliance with the mandate to decrease the use of freon-CFC propellants according to the Montreal Protocol.\textsuperscript{10} Furthermore, DPIs are breath-actuated and eliminate the need for coordination of inspiration and activation of the pressurized aerosol MDI.\textsuperscript{11} In
addition, MDI devices often require a spacer unit to help minimize uncoordinated inspiration and drug activation, while DPI systems do not. Lastly, DPI systems either have built in actuation counters or utilize a single unit dose format which eliminates continued use of an empty container.

However, there are areas where MDIs can be considered to compare favorably to DPIs. Several currently available DPI systems use single unit dosing and require reloading of the medication into a chamber with each administration; whereas MDIs contain up to 200 actuations in a single unit. If required for rescue treatment for relief of acute respiratory symptoms, a re-loading system for a DPI could be a problem. A drawback with the DPI system, not observed with the MDI, is that these non-pressurized devices cannot currently be used in intubated patients. In general, these issues with DPI systems arise from inconveniences and are not detrimental to the use or efficacy of the device under normal conditions.

The standard pressurized MDI has been repeatedly associated with performance problems in patients. Errors in performance may result in an inadequate or ineffective dose of medication delivered to the lung. As the deficiencies with the MDI have been recognized, alternative pressurized MDIs and DPI systems have been developed, to improve performance and delivery characteristics for inhalation devices. However, as with all devices, patient instruction is required and there is still a need to follow several steps for optimal use. Therefore, a formal evaluation of ability to use a device is required to adequately assess the device’s suitability for the intended patient population.

There have been reports evaluating the performance and adequacy of drug delivery from novel dry powder inhalation systems. In one 4-week study, the attributes and patient acceptability of the Accuhaler was compared with the pressurized MDI. In this 4-week study, patients preferred the Accuhaler over the MDI on the basis of ease of use. Another study of 318 patients with obstructive lung disease demonstrated that as many as 70% of patients made errors on inhalation technique with a dry powder device after receiving instructions. However, correct usage among health care professionals was the highest for the pressurized MDI compared with either the Turbuhaler (budesonide) or Diskus (salmeterol). Similarly, it was found that pharmacists were able to correctly demonstrate use for the MDI compared with the Turbuhaler. These findings support the concept that proper professional training is essential to increase the likelihood of proper patient technique independent of whether the device is an MDI or one of the different powder inhalers. Lastly, a comparison of the MDI and dry powder delivery of ipratropium was evaluated in COPD patients. The results of that study demonstrated equal efficacy for post drug improvements in FEV1 for both devices. In summary, the data from these trials suggest the need for clinical trials in order to evaluate patient acceptance, proper training and use of new inhalation devices for the delivery of bronchodilators.

The results of this study demonstrated that fewer mistakes were made with the HandiHaler device compared with the MDI. There were, however, limitations to this study. Device comparison was single blind, which is not atypical for these types of investigations. The trial was conducted over 4 weeks, which limited the exposure time of the patients to the devices. In addition, one of the devices had active medication (MDI) while the other (HandiHaler) held placebo; however, the bias here would favor the MDI. In the current study it is important to note that there was a problem with interpretation of one of the instruction steps for both HandiHaler and MDI use. In order to address this issue, we analyzed the data from the trial with and without the inclusion of this step (step 10 for HandiHaler and step 9 for MDI). The result was the same regardless of whether or not this step was included in the analysis. Finally, there were different frequencies of daily administration (q.i.d. vs. once daily), although, again, this should favor MDI performance. While patient ability to correctly use an inhalation device varies, there is clearly a need for improvement in the current design of the pressurized MDI systems to reduce the incidence of errors with medication delivery. For many years, MDIs have been the standard for inhalation therapy; however, in recent years the evidence suggests that patients can experience difficulty using all devices, which results in poor delivery of pharmacotherapy to the lung. The results of this study demonstrated that the ability of COPD patients to use the HandiHaler dry powder system was more easily learned with improved administration performance compared with the pressurized aerosol MDI system.

References


