Peak inspiratory flow through the Genuair® inhaler in patients with moderate or severe COPD

H. Magnussen a,*, H. Watz a, I. Zimmermann a, S. Macht a, R. Greguletzb, M. Falques c, D. Jarretac, E. Garcia Gil c

a Pulmonary Research Institute, Hospital Grosshansdorf, Center for Pneumology and Thoracic Surgery, Woehrendamm 80, 22927 Grosshansdorf, Germany
b Almirall Sofotec GmbH, Benzstrasse 1, D-61352 Bad Homburg v. d. Hoehe, Germany
c Almirall, R&D Centre, Laureá Miró 408-410, 08980 Sant Feliu de Llobregat, Barcelona, Spain

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Summary
The Genuair® inhaler is a novel multidose dry powder inhaler for the delivery of aclidinium bromide—a novel, long-acting, muscarinic antagonist in development for the treatment of chronic obstructive pulmonary disease (COPD). The primary aim of this study was to assess the inspiratory flow characteristics through Genuair® in patients with moderate or severe COPD.

Using a three-period cross-over design, 48 patients were randomised to inhale placebo powder through Genuair® , HandiHaler® A (slow, deep inhalation as per manufacturer’s instructions) or HandiHaler® B (fast, forceful inhalation). Three measurements of peak inspiratory flow (PIF), 10 min apart, were recorded for each method of administration.

The highest and average PIFs for the three attempts (mean ± standard deviation) generated through the Genuair® inhaler were 97.7 ± 15.7 and 92.0 ± 15.4 L/min, respectively. Furthermore, 97% of inhalations with the Genuair® inhaler were successful (activation of trigger threshold mechanism) and optimal (PIF ≥ 45 L/min). The highest and average PIFs generated through HandiHaler® A and B were significantly lower than with the Genuair® inhaler.

In conclusion, patients with moderate or severe COPD were able to generate sufficient inspiratory airflow through the Genuair® inhaler to reliably inhale the full dose and reset the inhaler.

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Introduction
Unlike pressurised metered-dose inhalers, dry powder inhalers (DPIs) do not require patients to coordinate
actuation with inhalation and are propellant-free. As a result of these advantages, DPIs are replacing pressurised metered-dose inhalers in the management of patients with chronic obstructive pulmonary disease (COPD). When using a DPI, patients are required to generate sufficient inspiratory flow to deagglomerate the powder into smaller particles for delivery to the airways. The inspiratory flow achieved by patients is dependent partly on their inspiratory effort and partly on the airflow resistance of the inhaler. Patients must invest a greater inspiratory effort to achieve the same inspiratory flow through a high-resistance inhaler compared with a low-resistance inhaler. Some patients with COPD may have problems generating sufficient inspiratory flow through a high-resistance inhaler. Therefore, when developing a new inhaler for the delivery of COPD medication, it is important to establish whether the target population can achieve an adequate inspiratory flow through the inhaler.

The Genuair inhaler (Fig. 1) is a new breath-actuated, multidose DPI for the delivery of aclidinium bromide, a novel, long-acting, muscarinic antagonist in development for the treatment of COPD. This inhaler has been designed to provide: multi-sensory feedback to the patient that a dose has been taken correctly; a trigger threshold function to prevent accidental double-dosing; and a lock-out mechanism that prevents further use of the inhaler after the last dose has been taken. The Genuair inhaler contains 1 month of therapy, requires no cleaning, and is disposable after all the doses have been delivered. A dose indicator tracks the doses, with a red strip appearing when the patient is close to the last dose.

This study assessed the inspiratory flow characteristics of the Genuair inhaler in patients with moderate or severe COPD. For comparison, an exploratory investigation of inspiratory flow through the HandiHaler, a single-dose DPI, was performed in the same patient population.

Methods

Study design

This was an open-label, randomised, cross-over study conducted at a single centre in Germany to assess the inspiratory flow characteristics of the Genuair inhaler. Eligible patients were enrolled within 7 days of the screening visit. Patients were trained in the correct use of the Genuair inhaler and the HandiHaler by written and verbal instruction. The steps required to use the Genuair inhaler and the HandiHaler are briefly described below.

For a correct inhalation through the Genuair inhaler, the patient must first remove the protective mouthpiece cap, then press and release the button on top of the inhaler to load a single dose into the powder inhalation chamber. The control window will simultaneously change from red to green to indicate that the inhaler is ready to use. The patient must then inhale through the mouthpiece to release the dose. Successful inhalation is indicated by an audible click, a slightly sweet taste that may be perceived by some patients, and the control window changing from green to red. In addition, once the button has been pressed and released, there is a 'trigger threshold' feature that prevents another dose from being loaded until after successful inhalation has occurred.

For a correct inhalation through the HandiHaler, the patient first must remove a capsule containing a single dose of medication from a package, open the mouthpiece of the inhaler and place the capsule in the centre chamber. After closing the mouthpiece, the patient must press a side button to pierce the capsule. The patient then inhales through the mouthpiece to deliver the medication. Finally, the mouthpiece is opened again and the used capsule is discarded. Confirmation of dose delivery is provided by hearing the capsule vibrate, tasting the powder and seeing the empty capsule.

When using the Genuair inhaler, patients were asked to inhale as fast and hard as possible. Inhaling through the HandiHaler were performed according to two different instructions: inhalation by a slow, deep breath, but at a rate rapid enough to hear the capsule vibrate, as per the manufacturer’s instructions (HandiHaler A), or inhalation as fast and hard as possible, simulating the instructions for use of the Genuair inhaler (HandiHaler B). Patients inhaled placebo powder through the three inhalers (Genuair inhaler, HandiHaler A and HandiHaler B) in a random order (six different sequences). For each inhaler, three measurements per patient were recorded at 10-minute intervals. During inhalation manoeuvres, the inhalers were connected to a spirometer through specially designed airtight adaptors.

The study was conducted in accordance with the Declaration of Helsinki, Principles for Correct Implementation of Clinical Trials, and International Conference on Harmonisation Good Clinical Practice Guidelines. An independent Ethics Committee approved the study and all patients provided written informed consent.

Patients

Male and non-pregnant female patients aged 40 yrs were eligible to enter the study if they had a diagnosis of moderate or severe COPD and stable airway obstruction. Patients were required to have a post-salbutamol forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) of <70% at screening. Half of the patients were required to have
moderate COPD, as defined by a post-salbutamol FEV₁ ≥ 50% and <80% of the predicted value, while the remaining patients were required to have severe COPD, as defined by a post-salbutamol FEV₁ ≥ 30% and <50% of the predicted value. All patients were current or previous cigarette smokers with a smoking history of at least 10 pack-yrs.

Patients were excluded for any of the following reasons: history or current diagnosis of asthma, allergic rhinitis or atopy; respiratory tract infection or COPD exacerbation within 6 weeks of the screening visit; hospitalisation for acute COPD exacerbation within 3 months of the screening visit; use of long-term oxygen therapy (>15 h/day); clinically significant respiratory conditions other than those related to the inclusion criteria; clinically significant cardiovascular conditions; clinically relevant medical findings or abnormalities unrelated to COPD; lactose intolerance; treatment with any investigational medical product within 1 month of screening.

The use of long-acting anticholinergic agents, long-acting inhaled β₂-agonists and sustained-release theophylline was prohibited for at least 72, 48 and 24 h, respectively, before the screening visit and study entry. Salbutamol was permitted as rescue medication during the washout period, but had to be discontinued at least 6 h before the screening visit and study entry.

Objectives

The primary objective of the study was to determine the peak inspiratory flow (PIF) generated through the Genuair® inhaler by patients with moderate or severe COPD. Secondary objectives were to determine the rate of successful and/or optimal inhalations with the Genuair® inhaler and the PIF generated through the HandiHaler® A and B.

Inhaler evaluation

PIF was measured using standard spirometry. Successful inhalation through the Genuair® inhaler was defined as an inhalation sufficient to activate the inhaler trigger and produce a colour change from green to red in the control window. Optimal inhalation through the Genuair® inhaler was defined as an inhalation that produced a PIF > 45 L/min, to ensure full dose inhalation based on unpublished in vitro data showing a constant fine particle dose between the flow rates of 45 and 95 L/min (Almirall, data on file 2009; Fig. 2). For each inhalation through the HandiHaler® A, capsule vibration heard by the investigator and powder remaining in the centre chamber of the inhaler were recorded (these endpoints were not assessed for HandiHaler® B).

Statistical analyses

All variables were summarised by means of appropriate descriptive statistics and were tabulated by inhaler group (Genuair® inhaler, HandiHaler® A and HandiHaler® B) for all patients and by COPD severity. The highest and average PIFs of the three attempts were assessed by an analysis of variance model for cross-over designs, with period, sequence, patient within sequence and inhaler as effect variables.

Results

Patients

A total of 48 patients with moderate (n = 24) or severe (n = 24) COPD were randomised and completed the study. Demographic and baseline characteristics of the study population are shown in Table 1.

<table>
<thead>
<tr>
<th>Table 1 Demographic and baseline characteristics by disease severity.</th>
<th>Moderate COPD (n = 24)</th>
<th>Severe COPD (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs</td>
<td>63 (±8.0)</td>
<td>65 (±6.7)</td>
</tr>
<tr>
<td>Male</td>
<td>18 (75)</td>
<td>18 (75)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>24 (100)</td>
<td>24 (100)</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>28.0 (±5.2)</td>
<td>29.2 (±6.7)</td>
</tr>
<tr>
<td>Duration of COPD yrs</td>
<td>8.3 (±9.5)</td>
<td>11.6 (±8.2)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>15 (62.5)</td>
<td>11 (45.8)</td>
</tr>
<tr>
<td>Smoking history pack-yrs</td>
<td>61.5 (±25.7)</td>
<td>55.0 (±24.3)</td>
</tr>
<tr>
<td>Post-salbutamol FEV₁ % of predicted value</td>
<td>59.5 (±6.9)</td>
<td>40.9 (±5.9)</td>
</tr>
<tr>
<td>Post-salbutamol FVC L</td>
<td>3.78 (±1.23)</td>
<td>3.27 (±0.79)</td>
</tr>
<tr>
<td>Post-salbutamol FEV₁/FVC ratio %</td>
<td>47.8 (±9.5)</td>
<td>37.7 (±8.9)</td>
</tr>
<tr>
<td>Salbutamol test % reversibility</td>
<td>19.3 (±15.1)</td>
<td>19.0 (±15.1)</td>
</tr>
<tr>
<td>Prior use of Novolizer®</td>
<td>4 (16.7)</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>Prior use of Handihaler®</td>
<td>17 (70.8)</td>
<td>21 (87.5)</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean (±sd) unless otherwise indicated.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; ±sd, standard deviation.
Peak inspiratory flow

In the overall population, the highest and average PIFs of the three attempts (mean ± standard deviation) generated through the Genuair® inhaler were 97.7 ± 15.7 L/min (Fig. 3) and 92.0 ± 15.4 L/min, respectively. The highest PIFs (mean ± SD) of the three attempts generated through HandiHaler® A and HandiHaler® B in the overall population were 51.2 ± 10.4 and 64.3 ± 8.7 L/min, respectively; these values were significantly lower than the highest PIF for the Genuair® inhaler in the same population (P < 0.001; Fig. 3). Similarly, the average PIFs of the three attempts generated through HandiHaler® A (46.1 ± 9.6 L/min) and HandiHaler® B (61.5 ± 8.9 L/min) were also significantly lower than for the Genuair® inhaler (P < 0.001).

When patients were stratified by disease severity, the highest PIFs (Fig. 3) and average PIFs were slightly greater for patients with moderate COPD compared with those with severe COPD for the Genuair® inhaler (9% and 7% difference, respectively), HandiHaler® A (3% difference for both) and HandiHaler® B (5% difference for both).

Individual patient data for the highest PIF of the three attempts for the Genuair® inhaler compared with HandiHaler® A and B are presented in Fig. 4a and b, respectively. These data show that patients consistently achieved a greater PIF when using the Genuair® inhaler compared with HandiHaler® A or B.

Evaluation of correct inhalation

Successful and optimal inhalations with the Genuair® inhaler

Overall, 97.2% (140/144) of inhalations with the Genuair® inhaler were successful and optimal. One patient with moderate COPD had an unsuccessful and suboptimal inhalation at the first attempt, with a PIF of 43.8 L/min. This patient successfully and optimally inhaled through the Genuair® inhaler on the second and third attempts, achieving PIFs of 58.8 and 61.2 L/min, respectively. For one patient with severe COPD, all three attempts were optimal but unsuccessful, despite generating PIFs between 61.8 and 91.8 L/min.

Capsule vibration and residual powder with HandiHaler® A

Capsule vibration and residual powder data for HandiHaler® A are shown in Table 2. The investigator heard...
capsule vibration after 81.3% (117/144) of the inhalations and no powder remained in the centre chamber after 78.5% (113/144) of the inhalations. No capsule vibration was heard and some powder remained in the centre chamber for 13.9% (20/144) of the inhalations.

Discussion

The PIF generated through the Genuair® inhaler by patients with moderate or severe COPD was significantly greater than that generated through the HandiHaler®, irrespective of whether patients inhaled through the HandiHaler® using a slow, deep breath (according to the manufacturer’s instructions) or using a fast, forceful breath, as for the Genuair® inhaler. PIF has been shown to be inversely proportional to the intrinsic resistance of an inhaler. Therefore, the results from this study confirm that the Genuair® inhaler has a lower flow resistance than the HandiHaler®, which translates to a lower inspiratory effort needed to produce a comparable PIF. The lower flow resistance associated with the Genuair® inhaler may benefit patients with COPD, particularly those with low inhalation capacity. Patients with moderate or severe COPD often have difficulty achieving sufficient inspiratory flow through DPIs with high resistance. Furthermore, the ability to generate sufficient inspiratory flow through a DPI appears to be compromised in elderly (>70 yrs) patients, which is of particular relevance since elderly patients account for a considerable proportion of patients with COPD. Therefore, the use of an inhaler with low to medium resistance, leading to achievable flow rates of typically 60–90 L/min, may be important in facilitating effective drug inhalation in patients with COPD.

Patients with moderate COPD are expected to be able to generate a higher PIF than those with severe COPD, and this difference is likely to be more obvious with a lower-resistance inhaler. Therefore, the slightly greater increases in highest and average PIF for the Genuair® inhaler vs. the HandiHaler® are consistent with the Genuair® inhaler having lower flow resistance than the HandiHaler®.

The PIF associated with the HandiHaler® in this study was slightly greater than that reported in a previous study of the inhaler in patients with moderate or severe COPD, where the highest and median PIFs were 45.6 and 30.0 L/min, respectively. This may reflect the fact that patients in the previous study had more severe lung obstruction (FEV1 16–65% of the predicted value) and were older (mean age 66.9 yrs) than patients in this study.

A high proportion (97.2%) of patients achieved optimal and successful inhalations through the Genuair® inhaler, confirming that the inhaler ensures reliable delivery with no risk of accidental double/multiple dosing. For the one attempt where the PIF generated was <45 L/min, the control window did not change colour from green to red. Therefore, in a real-life situation, the patient would have seen clearly that the inhalation was not optimal and should have inhaled again. In contrast, approximately one-quarter of inhalations through HandiHaler® A were performed incorrectly according to study criteria. A previous study of the HandiHaler® has shown that flow rates above 28.3 L/min are required for a consistent fine particle dose (Fig. 2). However, the lowest average PIF generated through HandiHaler® A by patients with severe COPD was 24.0 L/min, a flow rate at which insufficient dosing to the patient may occur (Fig. 2). By comparison, all patients inhaling through the Genuair® inhaler achieved an average PIF above that required in vitro for a consistent fine particle dose (Fig. 2). It must be noted that according to the manufacturer’s instructions, the patient should inhale twice through the HandiHaler® in order to empty the capsule completely, whereas the data presented in this study are for single inhalations through the HandiHaler® because the aim was to measure PIF. As there was some remaining powder in the centre chamber for almost a quarter (21.5%) of the single inhalations through the HandiHaler® in this study, these data support the requirement for two inhalations with the HandiHaler®.

A gamma scintigraphic study has assessed the lung deposition of a single dose of radiolabelled aclidinium 200 μg administered from the Genuair® inhaler at a mean (±SD) PIF of 79 (±9) L/min in 12 healthy males. The results showed that the Genuair® inhaler delivered aclidinium efficiently, with approximately 30% of the metered dose deposited in the lungs. Furthermore, lung deposition was consistent across the PIF range of 66–99 L/min. In a similar gamma scintigraphic study of radiolabelled tiotropium administered from the HandiHaler® in five healthy subjects and 15 patients with COPD, the lung deposition of tiotropium was approximately 20%, regardless of the presence or severity of COPD. Therefore, in conclusion, results from this study demonstrate that patients with moderate or severe COPD can achieve sufficient inspiratory airflow through the Genuair® inhaler to reliably inhale the full dose and reset the inhaler.

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Conflict of interest

H Magnussen has received funding for clinical research and received reimbursement for Advisory Board Meetings by Almirall.

H Watz has no conflicts of interest.
I Zimmermann has no conflicts of interest.
S Macht is an employee of Almirall.
R Greguletz is an employee of Almirall.
M Falques is an employee of Almirall.
D Jarreta is an employee of Almirall.
E Garcia Gil is an employee of Almirall.

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