Efficacy of formoterol Turbuhaler in the emergency treatment of patients with obstructive airway diseases

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Bronchoconstriction; Acute exacerbation of COPD; Dyspnoea; Pressurised metered dose inhaler; Turbuhaler

Summary
Dry powder devices are rarely used in the emergency room (ER) treatment of acute and severe bronchoconstriction due to hesitations with respect to clinical efficacy. This study investigated the effects of two inhalers with formoterol in patients visiting the ER Department for acute and severe dyspnoea, mainly exacerbations of chronic obstructive pulmonary disease. Two doses of 12 μg formoterol were given at enrolment, either via Turbuhaler or via pressurised metered dose inhaler, connected to a spacer device (pMDI+S) in a double-blind way and parallel design. Another two doses of 12 μg formoterol were given after 30 min. Forced expiratory volume in the 1 s (FEV1) and Borg dyspnoea score were assessed until 60 min. The study was designed to test non-inferiority in effects on FEV1. Seventy-seven patients were enrolled with a mean age of 66 years and a FEV1 of 1.03 L (39% of predicted). The effects of the two treatments were almost identical. The mean improvement in FEV1 at 60 min after formoterol Turbuhaler was 94% of the improvement after formoterol pMDI+S. A statistically significant non-inferiority was shown (p = 0.037) at 60 min (primary endpoint) as well as at 5 and 30 min (secondary endpoints, p = 0.0043 and 0.013, respectively). Improvements in the Borg dyspnoea score and other lung-function parameters did not differ significantly between the two devices. In conclusion, formoterol Turbuhaler was equally effective as formoterol pMDI+S in the treatment of acute bronchoconstriction within the ER.
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Introduction
Patients with obstructive airway diseases, such as asthma and chronic obstructive pulmonary disease (COPD) may experience episodes of bronchoconstriction, leading to
dyspnoea. Episodes of severe dyspnoea (exacerbations) form a frequent cause for unscheduled visits to health care professionals and emergency rooms (ERs).1,2

The current practice in the treatment of patients with severe acute exacerbations of asthma and COPD within the ER, is to administer high doses of a β-2 agonist either by nebulisation or by a pressurised metered dose inhaler, connected with a large volume spacer device (pMDI+S).2 The use of a dry powder inhaler device is assumed to be less effective in these patients due to the assumed reduced inspiratory flow through the inhaler, which is necessary to inhale adequately.3 However, in asthmatic patients, even in an acute and severe airway obstruction, inhalation via Turbuhaler has been proven to be as effective as inhalation via a pMDI+S.4,5 No such studies are available in the initial ER treatment of patients with severe exacerbations of COPD. Nevertheless, patients with stable COPD and patients with an acute and severe asthma exacerbation were able to generate a peak inspiratory flow (PIF) through the Turbuhaler, which would theoretically allow an efficient disintegration of drug particles from this device during inhalation.6,7

Formoterol is a β-2 agonist with a rapid onset of action, comparable to that of the traditional short-acting bronchodilators8,9 but it also has a long duration of effect.10 Recent studies showed the inhaled formoterol Turbuhaler to be more effective than both terbutaline and salbutamol when used “as needed” in both asthma and COPD.11-14 While formoterol Turbuhaler was used successfully in situations of acute dyspnoea in asthma,8 and in episodes of induced moderate bronchoconstriction in COPD,15 its use has not been investigated in episodes of severe bronchoconstriction in COPD, which would be required to fully trust the use of Turbuhaler under all circumstances.

The main research question of the present study was to test non-inferiority of the clinical effect of inhalation of formoterol Turbuhaler in comparison with formoterol inhaled via pMDI+S, in patients with severe dyspnoea visiting the ER. In our hospital, this category consists mainly of patients with an exacerbation of COPD.

Methods

Patients

Patients with acute and severe dyspnoea, presumed to be due to an exacerbation of obstructive airway disease, were asked to participate in this study, while presenting with an unscheduled visit, mainly at the ER and some in the outpatient clinic. Before entering the study the arterial blood gas values were assessed and an ECG and chest X-ray were taken, so that other causes of dyspnoea such as pneumoniae or cardiac failure were ruled out.

The most important inclusion criteria were an age above 18 years and a forced expiratory volume in 1 s (FEV1) of <70% of that predicted16 but more than 0.5 L. The diagnosis of obstructive airway diseases had to be present for at least 6 months, either confirmed by a general practitioner or by a pulmonologist. Excluded were patients with a known hypersensitivity to inhaled formoterol and those patients with significant concomitant diseases or conditions and those requiring immediate ventilator support.

At a later stage, after commencing the treatment, each patient’s medical record was checked in depth and the patient was assigned to the prior defined subgroup of “confirmed diagnosis of COPD” if age was >45, no history of concomitant or previous asthma was found, a smoking history of more than 15 pack years was documented and the postbronchodilator FEV1/FVC (forced vital capacity) ratio (determined in a stable situation for the past twelve months) was less than 0.70. All subjects gave written informed consent and the study was approved by the Medical Ethics Committee. A preliminary written informed consent was obtained upon arrival at the ER. A full-length written informed consent was obtained within 2 h after enrolment.

Study design

The study had a double-blind, randomised, parallel-group design using double dummy technique and was performed in a non-university teaching hospital. The study personnel, the pharmacist, the data-management personnel and the study monitor were blinded until ”clean file” was declared and the code was broken. To ensure optimal care, the study was performed only during daytime shifts. After the diagnosis ”acute and severe dyspnoea, likely to be due to an exacerbation of an obstructive airway disease” was made, other causes for dyspnoea were excluded and informed consent was obtained. The inhalation technique was briefly checked and when necessary corrected by the study personnel to ensure a correct inhalation technique. After assessing the baseline measurements of lung function and Borg dyspnoea score, the first dose of 24 μg formoterol (as 2 doses of 12 μg) was administered under supervision of the study personnel and the time was set at 0 min. Randomisation of study treatments was performed by a computer program. For each patient there was a package with one Turbuhaler and one pMDI plus spacer, one containing active medication and the other inhaler containing placebo.

Each patient received active formoterol, either via Turbuhaler (Oxis®, Turbuhaler®, 12 μg per metered dose, equivalent with 9 μg delivered dose, AstraZeneca, Sweden) or via pMDI (Foradil®, CFC metered dose inhaler, 12 μg per metered dose, Novartis, Switzerland) connected to a spacer device (Aerocamber®, Boehringer Ingelheim, Germany) and a placebo via the other device. The two pMDI’s and Turbuhalers had identical appearances. Half of the patients inhaled first from Turbuhaler, the other half first from pMDI+S. At 30 min, a second dose of two inhalations of 12 μg formoterol was given. For ethical reasons no placebo was included. Lung function and dyspnoea score were assessed at baseline and at 5, 15, 30 (prior to the second dose of formoterol), 45 and 60 min.

Measurements

Patients performed three acceptable forced expiratory measurements at all time points (portable spirometer Vitalograph 2120 and Jeager masterscreen), recorded sitting in an upright position and wearing a nose-clip. Three lung
function parameters were recorded: FEV₁, FVC and the mean forced expiratory flow between 25% and 75% of FVC (FEF₂₅–₇₅). At enrolment PIF was additionally measured. The highest values were recorded, whether or not from the same attempt. The predicted values of FEV₁ were calculated according to the ERS specification. After each lung function measurement, the patients were asked to score their dyspnoea on the Borg scale which ranges from 0 (= none) to 10 (= extreme). At baseline and after 60 min, blood pressure and pulse rate were measured. During the 1 h study period no concomitant bronchodilator therapy was given. Patients received oxygen, corticosteroids and antibiotics when needed. Administration of additional bronchodilator treatment in the first hour after the study-drug administration was allowed, but would be regarded as “treatment failure” and would lead to withdrawal from the study.

**Data analysis**

The primary analysis was aimed at investigating non-inferiority in effects on FEV₁. Treatment via the new treatment (Turbuhaler) was regarded to be non-inferior to the standard treatment (pMDI+S), when the mean increase in FEV₁ within the Turbuhaler group at 60 min including its lower one-sided 95% confidence interval (C.I.) would be greater than 85% of the mean increase in FEV₁ within the pMDI+S group. This 95% C.I. and the level of 85% were chosen in line with European guidelines on non-inferiority and were more demanding than the 80–125% limits usually required for bio-equivalence. Non-inferiority was tested statistically for the change in FEV₁ at 60 min (the primary parameter) and at 5 and 30 min. Secondary analyses were focussed on investigating the potential differences between treatments for the changes in FEV₁, FVC, FEF₂₅–₇₅ and the Borg score at a limited series of time points and for the areas under the curve (AUC) over the entire 60 min interval (AUC₀–₆₀) for FEV₁, FVC, FEF₂₅–₇₅ and the Borg score.

The statistical analysis was performed by analysis of variance (ANOVA) using a multiplicative model with the factor treatment, and the log-transformed baseline FEV₁ as percentage predicted as a covariate. Lung function data are expressed and analysed as the ratio at each time point relative to the value at 0 min and as the ratio of the effects Turbuhaler/pMDI+S. The least-squared means resulting from this model were used to calculate the one-sided 95% confidence interval for the log-transformed difference between the treatments: log(Turbuhaler) minus log(pMDI+S). These data were back-transformed to geometric means and its C.I. For the AUC₀–₆₀ and Borg data an additive ANOVA was used. Data of all patients were used in the statistical analysis but results are described separately for the subgroup of “confirmed diagnosis of COPD”, though without statistical comparison between treatments. The Pearson’s correlation coefficient was calculated for the relation between PIF and the treatment effect on FEV₁ within the two treatment groups. Assuming an actual effect of Turbuhaler relative to pMDI+S of >95%, 37 patients were calculated to be needed in each group in order to state non-inferiority with an alpha of 5% and a power of 80%.

**Results**

**Patients**

In total, 77 patients were enrolled and randomised in the period of June 2003–May 2005: 39 received treatment via Turbuhaler and 38 via pMDI+S. Two patients were withdrawn from the study, one because the FEV₁ was higher than allowed (more than 70% of predicted) and one patient due to malfunctioning of the spirometer. Demographic and baseline data of the two groups are shown in Table 1.

Patients were predominantly elderly men with a mean age of 66 years, having a significant smoking history of 32 pack years. At enrolment, 52 patients used inhaled corticosteroids, 61 patients a long-acting-β₂-agonist, 22 patients a long-acting anticholinergic agent and 12 patients were on oral theophylline. An oral corticosteroid course was started by the general practitioner in 22 patients in the last days prior to enrolment to this study. Medication use was similar in the two treatment groups.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic and baseline data.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Turbuhaler</td>
</tr>
<tr>
<td>Male/female</td>
<td>25/14</td>
</tr>
<tr>
<td>Age (year)</td>
<td>67.1 ± 13.3</td>
</tr>
<tr>
<td>”Confirmed diagnosis of COPD” (yes/no)</td>
<td>25/14</td>
</tr>
<tr>
<td>No/ex/current smoker</td>
<td>4/22/13</td>
</tr>
<tr>
<td>Pack years (only ex/current smokers)</td>
<td>30 (1–120)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 ± 6</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>0.98 ± 0.34</td>
</tr>
<tr>
<td>FEV₁ (% of predicted)</td>
<td>38.3 ± 12.6</td>
</tr>
<tr>
<td>Borg score</td>
<td>5 (1–10)</td>
</tr>
<tr>
<td>PIF (L/min)</td>
<td>196 ± 137</td>
</tr>
</tbody>
</table>

Data as mean ± SD, except for Pack years and Borg score: median (range).
pMDI+S: pressurised metered dose inhaler connected to a spacer; BMI: body mass index; FEV₁: forced expiratory volume in the 1 s; PIF: peak inspiratory flow.
At enrolment, dyspnoea was rated as “severe” (Borg Score 5) and FEV₁ was 1.03 L, equivalent to 39% of predicted. Forty-nine patients (64%) were eventually classified as having a “confirmed diagnosis of COPD”, 25 in the Turbuhaler group and 24 in the pMDI+S group. Lack of available lung-function data in the previous 12 months in a stable state and a smoking history of 10–15 pack years were the most common reasons (23 patients) to fail for classification for the “confirmed diagnosis of COPD”. After the study, five patients were later characterised as having primarily asthma by the pulmonologist.

The two treatment groups were comparable, except that the patients randomised to treatment via Turbuhaler were on average 2 years older and had at enrolment a 10% lower FEV₁ and a 10% lower PIF. Thirty-five patients were hospitalised after completion of the 1 h observation period (18 after Turbuhaler treatment and 17 after pMDI+S). None were admitted to medium or intensive care. None of the patients required additional bronchodilator therapy during the 1 h observation period, which would be classified as treatment failure.

Outcome measures

From enrolment, FEV₁ increased significantly and almost identically under both treatments. At 60 min the mean FEV₁ was 14.1% above the baseline in the group treated with formoterol via Turbuhaler and 20.0% in the group treated via the pMDI+S. After correction for differences in baseline, the relative effect of formoterol via Turbuhaler was 94% of the effect of formoterol via pMDI, the Turbuhaler/pMDI+S at 60 min became 0.94 with a lower limit of the one-sided 95% C.I. of 0.86 (p = 0.037), hereby showing treatment via Turbuhaler to be statistically significantly “non-inferior” to the pMDI+S.

Within the group of 49 patients with “confirmed diagnosis of COPD” the ratio Turbuhaler/pMDI+S was 0.98 (95% C.I. of 0.87–1.07). Results are depicted in Figure 1A (all patients) and B (“confirmed diagnosis of COPD” patients). Similar, non-inferiority was shown at 5 min (ratio 0.94, p = 0.0043, within the “confirmed diagnosis of COPD” subgroup the ratio was 0.98) and at 30 min (ratio 0.96, p = 0.013, within the “confirmed diagnosis of COPD” subgroup the ratio was 1.03).

The two treatments also induced similar effects in FVC and FEF₂₅₋₇₅. Results are shown in Table 2. At all tested time points the differences in treatment via Turbuhaler were shown to be non-significant compared to treatment via pMDI+S.

The three lung-function parameters were also analysed as AUC from 0 to 60 min. Both for FEV₁ and FVC the AUC values were not statistically significant different (p = 0.072 and 0.19, respectively), but for FEF₂₅₋₇₅, the AUC was significantly larger for the pMDI+S (p = 0.044).

Within 5 min after inhalation, the Borg score decreased in both treatment groups (Figure 2). The decrease in both, within the total study population and within the “confirmed diagnosis of COPD” subgroup was numerically larger after treatment via Turbuhaler, compared to pMDI+S, but the differences were not statistically significant. The AUC values for the Borg score were not significantly different (p = 0.28).

PIF at enrolment was on an average 207 L/min. The value of PIF did not show a significant correlation with the treatment effect (% increase in FEV₁ at 60 min), neither within the pMDI+S group (r = −0.08, p = 0.68) nor within the Turbuhaler group (r = −0.15, p = 0.44). These results are shown in Figure 3.

No treatment failures were noted, which were defined as the requirement of additional bronchodilator medication. Four patients, all in the pMDI group, experienced an adverse event (increased blood pressure in two patients, and chills and rales each in one patient). No serious adverse events occurred in the study.
Formoterol Turbuhaler in acute dyspnoea

Discussion

The present study was performed to investigate the relative efficacy of formoterol, inhaled via either Turbuhaler or pMDI+S in patients with severe dyspnoea due to obstructive airway diseases, treated in an ER Department in a double-blind, randomised, parallel-group design using double dummy technique. In these patients, a statistically significant non-inferiority of the Turbuhaler was shown, compared to a generally accepted method of administration of bronchodilators via pMDI+S. Almost identical effects were observed after inhaling the same dose through the two different inhalers for three objective parameters of lung function and for the subjective parameter dyspnoea, indicating that Turbuhaler was genuine and equally effective as the pMDI+S under these demanding circumstances of severe dyspnoea and bronchoconstriction. The effect on FEV₁ after inhaling formoterol through Turbuhaler in 5, 30 and 60 min was 94%, 96% and 94%, respectively, of the effect after inhaling through pMDI+S. The similarity in the clinical effect after the use of the two different devices indicates that the amount of formoterol reaching the lungs from the two different devices is similar. Patients were treated immediately upon arrival, as deemed necessary for ethical reasons. The precise diagnosis and historical lung function data, obtained in a stable phase in the previous 6 months, were established later and indicated that the majority of patients had exacerbations on top of a moderate to severe COPD. None of the patients required additional bronchodilating treatment during the 1 h observation period, which would indicate treatment failure, and a similar proportion of patients were hospitalised after the 1 h study for further (corticosteroid) treatment.

Both the onset of the effect and the magnitude of the effect, assessed via the various lung function parameters, measured in this study, were similar on all time points in the two treatment groups. For obvious reasons no placebo treatment group was incorporated in the present study and thus the absolute effect of inhaled formoterol in the present patient population cannot be assessed. A relatively low dose of only two inhalations of 12 μg was administered at enrolment, leading to similar bronchodilating effects immediately 5 min after inhalation, making it unlikely that lack of differences was caused by administering supra-maximal doses. The relative effects in the two treatment groups were so similar that missing a clinically relevant difference in effect is very unlikely.

It has been suggested that the effective use of a dry powder device is impossible in patients with a low-inspiratory flow, e.g. patients with an exacerbation of COPD. The results from the present study do not confirm this hypothesis. However, because of differences in the dry powder inhaler characteristics, one should be cautious to extrapolate this finding to all other dry-powder inhalers. It may be concluded however, that inspiratory flow is not as reduced as expiratory flow. Our present findings are in line with the earlier studies which showed that Turbuhaler can be used effectively in patients with an exacerbation of their asthma, and those of Dewar et al. who showed that patients with severe COPD can create a PIF which is theoretically high enough to use Turbuhaler efficiently. The rapid effects on lung function and dyspnoea confirm the findings of Maessen et al. and Cazzola et al. in patients with severe but stable COPD allowing study designs with assessments on subsequent test days. A recent study investigating lung deposition of formoterol Turbuhaler in patients with moderate-to-severe COPD showed that lung deposition was not related to the inspiratory-flow lung function parameters. The two treatment groups were comparable, except that the patients randomised to treatment via Turbuhaler were older and had a more severe disease, as shown from a 10% lower FEV₁ and PIF. This could have favoured the pMDI+S group, since older patients and those with a more severe

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Turbuhaler all patients</th>
<th>PMDI+S all patients</th>
<th>Turbuhaler &quot;confirmed diagnosis of COPD&quot;</th>
<th>PMDI+S &quot;confirmed diagnosis of COPD&quot;</th>
<th>p-Value for non-inferiority, all patients</th>
<th>p-Value for difference, all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁</td>
<td>1.09 ± 0.13</td>
<td>1.13 ± 0.11</td>
<td>1.08 ± 0.18</td>
<td>1.08 ± 0.13</td>
<td>0.004</td>
<td>0.080</td>
</tr>
<tr>
<td>FEV₁</td>
<td>1.12 ± 0.19</td>
<td>1.13 ± 0.17</td>
<td>1.12 ± 0.22</td>
<td>1.09 ± 0.13</td>
<td>0.013</td>
<td>0.48</td>
</tr>
<tr>
<td>FEV₁</td>
<td>1.14 ± 0.19</td>
<td>1.20 ± 0.20</td>
<td>1.12 ± 0.20</td>
<td>1.15 ± 0.15</td>
<td>0.037</td>
<td>0.29</td>
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<tr>
<td>FEF₂₅–₇₅</td>
<td>1.07 ± 0.30</td>
<td>1.14 ± 0.29</td>
<td>1.11 ± 0.30</td>
<td>1.06 ± 0.28</td>
<td>n.t.</td>
<td>0.055</td>
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<tr>
<td>FEF₂₅–₇₅</td>
<td>1.06 ± 0.30</td>
<td>1.24 ± 0.45</td>
<td>1.05 ± 0.25</td>
<td>1.16 ± 0.45</td>
<td>n.t.</td>
<td>n.t.</td>
</tr>
<tr>
<td>FVC</td>
<td>1.12 ± 0.15</td>
<td>1.15 ± 0.24</td>
<td>1.15 ± 0.17</td>
<td>1.13 ± 0.24</td>
<td>n.t.</td>
<td>0.41</td>
</tr>
<tr>
<td>Borg at 5</td>
<td>0.58 ± 1.08</td>
<td>0.43 ± 0.92</td>
<td>0.64 ± 1.22</td>
<td>0.33 ± 0.73</td>
<td>n.t.</td>
<td>0.92</td>
</tr>
<tr>
<td>Borg at 10</td>
<td>1.17 ± 1.53</td>
<td>0.68 ± 1.32</td>
<td>1.00 ± 1.53</td>
<td>0.46 ± 0.96</td>
<td>n.t.</td>
<td>0.15</td>
</tr>
<tr>
<td>Borg at 60</td>
<td>1.38 ± 1.67</td>
<td>0.85 ± 1.51</td>
<td>1.20 ± 1.58</td>
<td>0.63 ± 1.17</td>
<td>n.t.</td>
<td>n.t.</td>
</tr>
</tbody>
</table>

Data on 77 patients (mean ± SD) randomised to treatment via Turbuhaler (n = 39) or pressurised metered dose inhaler with spacer (pMDI+S) (n = 38). Data is expressed as changes from the values at 0 min, for lung function as the ratio and for the Borg score as the decrease from the data at 0 min.

FEV₁: forced expiratory volume in the first second; FVC: forced vital capacity; FEF₂₅–₇₅: forced expiratory flow between 25% and 75% of FVC; n.t: not tested; no statistical comparison within the subgroup with "confirmed diagnosis of COPD" was foreseen.

*Primary parameter; "confirmed diagnosis of COPD", see text.
COPD may be expected to show the smallest reversibility, but it seems unlikely that these differences influence the outcome of the study. Additionally, baseline lung function was used as the covariate in the statistical analyses.

The AUC of the FEF_{25-75} was significantly larger in the pMDI+S group, mainly due to one person with an extreme positive reaction after formoterol inhalation, who was later diagnosed as having primarily asthma.

Interestingly, the changes in the Borg score, both in the "confirmed diagnosis of COPD" and in the total study population were numerically larger (almost two-fold) after inhalation via Turbuhaler compared to inhalation via pMDI+S. Though the study was performed with the double dummy technique and placebo inhalers, this may indicate that a sensed inhalation is not a requirement for a subjective effect.

In conclusion, our study is to present knowledge the first study, examining the use of a dry powder inhaler (such as the Turbuhaler) in patients visiting the ER Department with acute and severe dyspnoea due to an exacerbation of obstructive airways. It was shown that the Turbuhaler was an equally effective inhaler as the pMDI+S in delivering the bronchodilator formoterol, even in the "confirmed diagnosis of COPD" subgroup. These results give confidence for patients using the Turbuhaler as a rescue medication, even in these circumstances.4,5,14,23

Acknowledgements

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