Lung deposition and efficacy of inhaled formoterol in patients with moderate to severe COPD

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Received 21 January 2007; accepted 16 April 2007
Available online 1 June 2007

Summary
Background: Little is known about the impact of COPD on lung deposition of inhaled drugs and the relationship between lung-dose and response of pulmonary function measurements.
Methods: Nineteen patients with varying degrees of COPD were randomized to inhale single doses of formoterol (Oxis\textsuperscript{R}) Turbuhaler\textsuperscript{R} 4.5, 9, 18, and 36\textmu g in a double blind, placebo-controlled, crossover design. Urinary excreted formoterol during 32 h was used to determine absolute lung deposition. Peak inspiratory flow (PIF) and inhaled volume (IV) were recorded to assess the patients’ ability to use Turbuhaler. Efficacy was measured by spirometry, inspiratory capacity (IC), airway conductance (sG\textsubscript{AW}), and absolute lung volumes.
Results: Mean pulmonary bioavailability of formoterol was about 24% of the nominal delivered dose after inhalation for the different treatments. No significant correlations between lung deposition and baseline FEV\textsubscript{1}, PIF or IV were shown. All formoterol doses produced statistically significant increases in FEV\textsubscript{1}, FVC, IC, and sG\textsubscript{AW} relative to placebo. Linear dose/response relationships were observed for these variables, with more narrow limits of the slopes for the lung-dose/response relationships than for the nominal-dose/response relationships. Moreover, 36 and 18\textmu g formoterol statistically significantly decreased functional residual capacity (FRC) and residual volume (RV) relative to placebo.
Conclusions: This study could not show any difference in lung deposition of formoterol inhaled via Turbuhaler between patients with moderate and severe COPD. Moreover, the...
Introduction

Studies on lung deposition of inhaled bronchodilators conducted in healthy subjects and in patients with asthma have shown that the portion of the delivered drug deposited in the airways is dependent on device characteristics and inhalation technique. According to current Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, inhaled short- and long-acting bronchodilators are the first choice in the medical treatment of patients with moderate to severe chronic obstructive pulmonary disease (COPD), since they improve symptoms, spirometric indices, exacerbations, and quality of life. COPD patients are characterized by airway obstruction, hyperinflation, mucus hypersecretion, and pronounced disturbances in distribution of ventilation, which is far more inhomogeneous than in asthmatics. Therefore, uncertainty exists concerning the penetration and deposition of inhaled drugs in the airways of patients with COPD.

To the best of our knowledge, the deposition and fate of inhaled drugs have not previously been systematically investigated in COPD patients. If anything, discrepant data have been reported in this area. Two studies showed that pulmonary deposition of radioactive particles appeared to be somewhat related to FEV1 in patients with COPD, whereas another study was unable to demonstrate any difference in total and regional lung deposition of inhaled ipratropium bromide between healthy subjects and patients with severe COPD.

The present study was designed to assess inhalation performance, lung deposition and efficacy of formoterol (Oxis®), administered via a dry powder inhaler (Turbuhaler®) in patients with COPD. The primary outcome was lung deposition, determined as the absolute pulmonary bioavailability of formoterol. Secondary objectives were the effects of different inhaled formoterol doses on a variety of pulmonary function variables, the relationship between lung deposition and effect of formoterol on pulmonary function, the potential influence of the degree of severity of COPD on total lung deposition of formoterol, and the patient’s ability to inhale via Turbuhaler.

Patients, methods and study design

Patients

Patients were to be between 40 and 80 years of age, have a clinical diagnosis of COPD with symptoms for at least 2 years and be current or previous smokers with a smoking history of at least 10 pack years. Only patients with stable COPD (i.e. no significant exacerbation, defined as hospitalization, a course of antibiotics or an increase in inhaled/oral corticosteroid dosage 2 months prior to entry into the study) were to be included. They should exhibit a baseline FEV1 of less than 80% predicted and at least 800 mL, and a FEV1/FVC ratio below 70%. Patients with a history of asthma or allergic rhinitis and patients with COPD under long-term oxygen therapy were to be excluded. Signed informed consents were to be obtained. The study was performed in accordance with the declaration of Helsinki and approved by the Ethics Committee of Ghent University Hospital and the National Board of Health and Welfare in Belgium. The first patient was enrolled on 19 July 2001, the last subject completed the study on 5 May 2003.

Study design

The study was of placebo-controlled, double blind, double dummy and had a partly randomized, six-period crossover design. The study included eight visits and a telephone contact for adverse events (Fig. 1). Eligibility was assessed at Visit 1, and baseline pulmonary function measurements were performed at Visit 2. Placebo and single doses of 4.5, 9, 18, and 36 μg formoterol Turbuhaler (dose strengths being expressed as nominal delivered dose) were randomly administered on five different study days (Visits 3–5, 7, and 8) by inhalations of Oxis® Turbuhaler 4.5 μg and/or lactose-containing placebo Turbuhaler. A single intravenous dose of formoterol was given over 5 min at Visit 6. The study drug administrations were separated by a washout period of at least 1 and no more than 3 weeks.

The inhalation technique was practiced using placebo at Visit 2 and refreshed before inhaled drug administration at

Patients, methods and study design

Patients

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each other visit. Patients were asked to inhale deeply and forcefully in standing position and were trained to reach a peak inspiratory flow (PIF) of at least 60 L/min within 0.5 s. Before use, Turbuhaler inhalers were primed by holding the inhalers in an upright position and turning the grip three times back and forth. The third dose was then inhaled. Inhalations took place in a separate room. The patients and clinical staff wore protecting gloves during inhalation to avoid contamination of urine samples with formoterol. The patients performed eight inhalations per visit, with one dose of formoterol/placebo from each of the eight inhalers and approximately 30 s in between. Formoterol was always administered before placebo to minimize the potential impact of the time factor between inhalations of formoterol on pulmonary deposition.

PIF and inhaled volume (IV) generated during inhalation through Turbuhaler were measured by connecting the inhaler to a Vitalograph Compact 1 MDI spirometer (Vitalograph Ltd., UK). Patients were instructed to breathe out calmly, close their lips around the mouthpiece, and take one forceful and deep breath. Thereafter, they put down the inhaler, and breathed out through the nose. After inhalation of the study drug, the patients washed their hands and the outside of their mouth before leaving the drug administration room. Two batches of formoterol Turbuhaler were used, which had fine particles fractions (<5 μm) of 51% and 54%.

In order to prevent oropharyngeal and gastrointestinal absorption, activated charcoal was given orally as an aqueous slurry (Carbomix®, Selena Fournier) at all study visits as described before. The following protocol was used: 5 mg immediately before the start of inhalation or infusion, 5 mg immediately after inhalation or infusion, 10 g 1 h and 10 g 2 h after the start of inhalation or infusion. This has been shown to completely block gastro-intestinal absorption of orally administered formoterol (AstraZeneca, data on file).

In the morning of Visit 6, 10μg formoterol fumarate dihydrate (2 mL formoterol fumarate dihydrate solution for injection, 5 μg/mL) was administered manually, over 5 min, at a constant rate via an indwelling catheter. The weight of the syringes was recorded before and after infusion.

At Visits 3–8, urine was collected up to 32 h after administration of the study drug for determination of amount excreted formoterol.

Pulmonary function measurements were performed at Visit 2 (baseline) and at Visits 3–5 and 7–8, before and 1.5 h after inhalation of the study drug.

Methods

Lung deposition
The total amount of formoterol excreted in urine, up to 32 h after administration was used to determine lung deposition. There is no evidence of local metabolism of formoterol in the human lung and the orally administered charcoal completely blocks the gastro-intestinal uptake of the portion of formoterol deposited in the oropharynx. Thereby, an estimate of systemic bioavailability, such as the dose-corrected ratio of urine recovery after inhalation and intravenous administration, equals the lung deposition of inhaled formoterol.

At Visits 3–8, patients were asked to empty their bladder just before inhalation or infusion of the study drug and aliquots of this urine were saved for baseline analysis. Thereafter, urine was collected quantitatively in two fractions, 0–6 and 6–32 h after administration of the study drug. Aliquots from each urine fraction were stored at −20 °C until analysis.

The urine samples were analyzed at Quintiles AB, Analytical Services, Uppsala, Sweden using a coupled column LC-electrospray ionization (ESI)-MS/MS method with a 2H4-labeled analog as internal standard to determine the concentration of formoterol. The method was calibrated over the concentration range 0.0400–50.0 nM with a lower limit of quantification (LOQ) of 0.0400 nM.

One (1.00) mL urine, 100 μL internal standard (2H4-labeled analog) solution and 0.1 M ammonium acetate buffer pH 5.0 were mixed. The samples were transferred to conditioned solid phase extraction columns (Isolute C18, 200 mg, 3 mL) where the extraction was performed. The eluates were evaporated to dryness. The residue was dissolved in 250 μL 10% methanol and 0.5% acetic acid in water. After mixing, the samples were centrifuged and aliquots of the centrifuged samples were injected onto the LC-ESI-MS/MS. The columns used in the coupled column LC system were as follows: Column 1: Phenomenex LUNA CN, 5 μm, 50 × 2.0 mm; Column 2: Jones Chromatography Genesis C18, 4 μm, 10 × 2.1 mm; Column 3: Hibichrome ACE C18, 3 μm 50 × 2.1 mm. Formoterol and the internal standard were detected by using ESI positive ion multiple reaction monitoring (MRM) of the transitions m/z: 345.00–149.20 (formoterol) and 349.00–153.30 (internal standard). The mean accuracy values from the quality control samples at 0.100, 10.0 and 40.0 nM were 104%, 100% and 99%, respectively, and the corresponding precisions were 4.6%, 1.8% and 2.9%, respectively. The lower limit of quantification (LLOQ) was 40 pmol/L. The interassay coefficient of variation was up to 4.6%. For urine concentrations below the LLOQ, the concentration value was set to zero.

For each portion of urine the amount of excreted formoterol was calculated as formoterol concentration times urine volume, corrected for urine density (1020 g/L). The fraction of formoterol excreted in urine was calculated as the quotient between the total amount of formoterol excreted within 32 h and the administered dose of formoterol. The nominal dose of formoterol was used for inhaled treatments. The infusion volume times the actual batch concentration was used for the intravenous dose. Infusion volume was determined from the difference in syringe weight before and after infusion, corrected for the density of the solution (1.005 g/ml). Furthermore, the intravenous dose was corrected for a 0.4% adsorption of formoterol in the infusion tube.

Lung deposition, determined as absolute pulmonary bioavailability (Fpulm), was calculated as the dose-corrected ratio of the total amount of formoterol excreted over 32 h after inhaled and intravenous treatments. The lung dose of formoterol after inhaled treatment was calculated as the nominal dose times the lung deposition.
Pulmonary function

Pulmonary function measurements were performed according to the ERS Guidelines. Efficacy was measured by means of spirometry, inspiratory capacity (IC), functional residual capacity (FRC), residual volume (RV), total lung capacity (TLC), and specific airway conductance \( sG_{aw} \), which have all been used as a marker for bronchodilatation in COPD. The same technician measured the parameters at approximately the same time of the day.

Spirometry (FEV1 and FVC) was performed after a 15 min rest, using the pneumotachograph of a bodyplethysmograph (Jaeger Masterlab, Würzburg, Germany). The highest FEV1 and FVC obtained from at least three acceptable forced expiratory maneuvers were retained. Based on their FEV1, patients were stratified into two groups with baseline FEV1 between 50% and 80% predicted and below 50% predicted.

Measurements of IC, FRC, RV, and TLC were performed, using the helium dilution technique. Patients were in sitting position and wore a nose clip. A constant volume bodyplethysmograph (Jaeger Masterlab, Würzburg, Germany) was used to measure airway resistance \( R_{aw} \) and \( sG_{aw} \).

A reversibility test was performed after spirometry at Visit 1 by measuring FEV1 at 30 min after four inhalations of salbutamol 100 μg and four inhalations of ipratropium 40 μg from pMDIs connected via a large volume spacer.

Restrictions

Smoking was not allowed from 1 h before drug administration to 4 h after administration, nor were caffeinated beverages from 8 h before drug administration to 4 h after administration. Intake of food and liquids were not permitted 1 h prior to and 4 h after administration of study drug, except water, which was allowed after intake of charcoal scheduled one hour after study drug administration. Patients were forbidden to do any strenuous physical exercise within 2 h before administration of the study drug to completion of the visit.

At least 30 days before Visit 1 and during the study period, inhaled and oral corticosteroid therapy was kept constant and administered at approximately the same time of the day. Oral and inhaled long-acting \( \beta_2 \)-agonists, tiotropium, and theophylline were discontinued for at least 48 h prior to all the visits, as were inhaled short-acting \( \beta_2 \)-agonists, inhaled ipratropium bromide for at least 8 h prior to all visits. Leukotriene antagonists, \( \beta \)-blocking agents, including eye drops, and any medication containing ephedrine were not allowed during the study. Ipratropium bromide pMDI 40 μg/dose was to be used as rescue medication.

Statistical analysis

The statistical analysis was performed at AstraZeneca R&D Lund using Gauss from Aptech Systems Inc. (Gauss Kernel revision: 5.0.16) and the Rieman Library (version 2.0.0). All data were used for analysis, regardless whether a patient had quantifiable concentrations of formoterol in the predose urine samples or not. All hypothesis testings were performed using two-sided alternative hypotheses. \( P \)-values less than 5% were considered statistically significant.

Absolute pulmonary bioavailability was estimated for the different pulmonary function efficacy variables (FEV1, FVC, IC, FRC, RV, TLC, and \( sG_{aw} \)) and the Rieman Library (version 2.0.0). All data were used for analysis, regardless whether a patient had quantifiable concentrations of formoterol in the predose urine samples or not. All hypothesis testings were performed using two-sided alternative hypotheses. \( P \)-values less than 5% were considered statistically significant.

The effect of inhaled formoterol on pulmonary function was compared between treatments using multiplicative ANOVA models with patient, period and treatment as fixed factors, and using baseline of the study as covariate. When comparing active treatments with placebo, the highest dose of formoterol was first compared with placebo and, if this difference was statistically significant, then decreasing doses of formoterol were compared until the placebo difference was no longer statistically significant.

Nominal-dose/response relationships for FEV1, FVC, IC, RV, TLC, and \( sG_{aw} \) were investigated by fitting straight lines to the adjusted means (on the log scale) vs. logged nominal dose using weighted linear regression. Relationships between lung dose and the different pulmonary function variables were expressed using mixed effect modeling. A linear mixed model with random factor patient and with fixed intercept and slope for the covariate (i.e. logged lung dose) was used. Both models with effect measured on the log scale (logged baseline ratios) and with effect measured on the linear scale (baseline difference) were used.

Relationships between PIF and IV during inhalation via Turbuhaler and baseline FEV1 were described graphically and expressed by linear mixed effect models. Relationships between lung deposition and PIF, IV, or baseline FEV1 were described and expressed in the same manner.

Results

Patient characteristics

Nineteen (18 male) patients were included. Their demographic and baseline characteristics at Visit 1 are summarized in Table 1. All patients were older than 40 years of age, had a diagnosis of COPD, and had at least smoked 10 pack years. None had the diagnosis of asthma. Of the 19 randomized patients, 11 had a baseline FEV1 between 50% and 80% predicted and eight had a baseline FEV1 below 50% predicted. The majority of the patients were hyperinflated with a median FRC of 131% (range: 73–217%) predicted. Most patients were on inhaled glucocorticosteroids at randomization. There were no dropouts, other than patient No. 1, who was withdrawn from the study after Visit 5, as he developed a cerebrovascular accident. Some of his pulmonary function data could be used, but absolute bioavailability could not be assessed, since he never attended Visit 6.

Inhalation characteristics

PIF and IV via Turbuhaler were measured for each of the eight inhalations at all study visits with inhaled treatments, in total 744 inhalations. Mean PIF of all values was 59 L/min (patient range: 45–73 L/min) and mean inhalation volume was 2.20 L (patient range 1.39–3.42 L). PIF and IV were not
affected by the number of inhalations, both variables remaining stable during the inhalation of the eight doses. The variability in PIF and IV was higher between than within patients. Mean IV increased statistically significantly with increased baseline FEV₁ (Fig. 2, slope value 0.017 with C.I. between 0.009 and 0.025). Although mean PIF tended to be slightly higher in patients with higher FEV₁, the correlation was not statistically significant (Fig. 2, slope value 0.130 with C.I. between −0.007 and 0.266), the mean difference between patients with a FEV₁ of 30% and a FEV₁ of 70% being less than 6 L/min (Fig. 2). A higher PIF was statistically significantly correlated with a higher IV (Fig. 2, slope value 0.024 with C.I. between 0.012 and 0.036).

**Lung deposition**

All patients had formoterol concentrations above LLOQ in the 0–6 h urine samples and 13 of the 18 patients had concentration values above LLOQ in the 6–32 h urine samples at all dose levels. The concentrations below LLOQ in the 6–32 h urine samples were all found after administration of the lowest dose, 4.5 μg. The mean fraction of excreted unchanged formoterol in urine was 17.2% of the 10 μg intravenously administered dose. After inhalation of 4.5, 9, 18, and 36 μg formoterol, the fractional excretion of unchanged formoterol in urine was 3.6%, 4.7%, 4.2%, and 3.9% of the nominal dose, respectively, giving mean estimates of lung deposition ranging between 20.5% and 27.0% (Table 2). Mean lung deposition based on all four dose levels was 24.0%. Dose proportionality in lung deposition of

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**Table 1** Demographic and lung function data.

<table>
<thead>
<tr>
<th></th>
<th>Median (minimum–maximum)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>64 (44–81)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25 (19–32)</td>
</tr>
<tr>
<td>Pack-years</td>
<td>30 (10–45)</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>1.64 (0.95–2.43)</td>
</tr>
<tr>
<td>FEV₁ (%)</td>
<td>54 (33–70)</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.38 (1.83–4.73)</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>82 (50–104)</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>51 (37–64)</td>
</tr>
<tr>
<td>Reversibility (% baseline)</td>
<td>16 (2–41)</td>
</tr>
<tr>
<td>Reversibility (% predicted)</td>
<td>8 (1–17)</td>
</tr>
<tr>
<td>FRC (% predicted)</td>
<td>131 (73–217)</td>
</tr>
<tr>
<td>RV (% predicted)</td>
<td>151 (83–241)</td>
</tr>
<tr>
<td>TLC (% predicted)</td>
<td>104 (75–136)</td>
</tr>
<tr>
<td>sGAW (1 kPa⁻¹ s⁻¹)</td>
<td>0.29 (0.11–0.53)</td>
</tr>
</tbody>
</table>

**Table 2** Absolute pulmonary bioavailability of formoterol (% of nominal dose).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adjusted means</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formoterol 4.5 μg</td>
<td>20.5</td>
<td>4.8–100.7</td>
</tr>
<tr>
<td>Formoterol 9 μg</td>
<td>27.0</td>
<td>8.4–116.4</td>
</tr>
<tr>
<td>Formoterol 18 μg</td>
<td>24.4</td>
<td>11.1–41.2</td>
</tr>
<tr>
<td>Formoterol 36 μg</td>
<td>23.7</td>
<td>12.6–36.6</td>
</tr>
</tbody>
</table>

**Figure 2** PIF (upper left-hand pannel) and IV (upper right-hand pannel) during inhalation of formoterol Turbuhaler, as a function of baseline FEV₁. IV during inhalation of formoterol Turbuhaler, as a function of PIF (lower pannel).
formoterol was indicated since the slope of the line between lung and nominal dose was not statistically different from zero (slope value 0.049% with 95% C.I. between −0.091 and 0.188).

A few high pulmonary bioavailability values were found after inhalation of the two lowest doses (Fig. 3). Patient No. 3 had a lung deposition value of 76% after inhalation of 9 μg formoterol and patients Nos. 13 and 18 had deposition values of 101% and 116% after inhalation of 4.5 and 9 μg, respectively. These three patients had formoterol above the LLOQ in their baseline samples and an abnormally high amount of formoterol excreted within 6–32 h, despite the required temporary discontinuation of all formoterol treatments before each study visit. Since the erroneous intake of formoterol before and immediately after the study visits could lead to an overestimation of the deposition data, a sub-analysis was performed in those patients, that had no detectable formoterol in their predose urine samples. This yielded mean lung depositions of 17.6% (range: 8.4–34.2%), 23.0% (range: 11.1–41.2%), and 23.8% (range: 12.6–33.6%) of the nominal dose for the 9, 18 and 36 μg dose, respectively, and 12.4% (range: 5.1–39.5) for the 4.5 dose. In these “clean” patients, concentrations of formoterol were below the LLOQ in the 6–32 h urine fraction in half of the patients after inhalation of the 4.5 μg dose, explaining the low deposition after 4.5 μg.

The influence of different covariates on lung deposition of formoterol was investigated assuming dose-independent lung deposition of formoterol. Linear mixed effects models were fitted to the data. No statistically significant linear correlations were observed between disease severity, determined as baseline FEV1 at Visit 2 and lung deposition, expressed as percentage of nominal dose (Fig. 3). Mean deposition averaged 24.8% (95% C.I.: 21.7–28.3) of the delivered dose for the patients with baseline FEV1 between 50% and 80% predicted and 23.3% (95% C.I.: 19.3–28.3) for patients with baseline FEV1 below 50% predicted. Moreover, no statistically significant linear correlation was observed between lung deposition of formoterol and reversibility at Visit 1, PIF or IV during the inhalation maneuver.

Effects on pulmonary function

Changes in pulmonary function, measured before and 1.5 h after inhalation of placebo and formoterol 4.5, 9, 18, and 36 μg are presented as geometric mean baseline ratios for FEV1, FVC, IC and sGaw (Fig. 4). FEV1 increased by 8.4% (0.14 L), 8.0% (0.14 L), 13.2% (0.22 L), and 18.6% (0.32 L) from baseline after inhalation of 4.5, 9, 18, and, 36 μg formoterol via Turbuhaler, respectively, whereas FEV1 remained stable (−0.03 L) after placebo. Similar statistically significant dose-dependent changes were observed for FVC, IC, and sGaw. All formoterol doses induced statistically significant increases in FEV1, FVC, IC, and sGaw, compared to placebo. RV and FRC decreased statistically significantly at the 18 and 36 μg formoterol dose compared to placebo.

Relationship between nominal-dose and pulmonary function variables

Dose/response relationships were investigated for FEV1, FVC, IC, and sGaw (Fig. 4). Statistically significant correlations between nominal dose and effect were observed for FEV1, FVC, IC, and sGaw (Table 3), whether the changes were

Figure 3 Lung deposition (determined as absolute pulmonary bioavailability, \( F_{\text{pulm}} \)) of formoterol inhaled via Turbuhaler as a function of baseline FEV1 (upper right-hand panel), PIF (upper left-hand panel) and IV (lower panel).
expressed as percentage from baseline or as absolute change between pre and post dose.

Relationship between lung-dose and pulmonary function variables

Statistically significant correlations between lung-dose and pulmonary function variables were found for FEV1, FVC, IC, and sGAW (Fig. 5). Similar results were obtained, if absolute changes in pulmonary function were used. The 95% confidence intervals were more narrow for the lung-dose/response relationships than for the nominal-dose/response relationships, indicating that the effects on pulmonary function were better described by lung deposition than by nominal dose.

Adverse events

One patient was hospitalized between Visit 5 and 6, because of stroke. This event, though serious, was not considered to be related to the study drug. Similarly, another patient was hospitalized for a cholelithiasis.

Discussion

Lung deposition

The present study showed that about 24% of formoterol delivered via Turbuhaler is deposited in the lungs of patients with moderate and severe COPD. In addition, the effects on pulmonary function were related to both the nominal dose
of formoterol and the amount deposited in the lung, with a closer relationship to the latter. This suggests that lung deposition may be used as a surrogate marker for the clinical effects of inhaled formoterol in COPD, in line with what has previously been shown for a number of drugs in patients with asthma. A pertinent finding is that no correlation between baseline FEV1 and lung deposition was observed.

The reliability of urinary data is important in determining the accuracy of the lung deposition and the validity of the correlations between lung deposition and pulmonary function variables. Factors that could have interfered with the accuracy of the lung deposition data were: incompleteness of the urine collections, mistakes in discontinuation of formoterol therapy by the patients immediately before and after the study days, and inability to detect urinary concentrations of formoterol below the LLOQ.

In order to ensure completeness of the urine collections, patients remained under close supervision at the clinic for the first 6 h after study drug administration—(a time interval during which 60–70% of the formoterol is expected to be excreted). Of the 108 urine collections performed outside the hospital, only one (placebo) was documented to be incomplete.

Three patients showed extremely high lung deposition values on one occasion each. Only not permitted use of formoterol might explain these values. Two of these patients were on regular treatment with formoterol before entering the study, and apparently did not interrupt their treatment in time or resumed the inhalation of formoterol too early, i.e. before completion of the 6–32 h urine collection. This is supported by the analysis of the urine, obtained pre-dose at Visits 3–8, which contained formoterol. However, the impact of this overestimation of individual lung deposition on mean lung deposition appeared to be of limited importance. A sub analysis of the patients in whom no formoterol could be detected in the pre-dose urine did not invalidate our conclusions, since lung deposition values of formoterol Turbuhaler in these patients ranged between 18% and 24% of the delivered dose, at least for the three highest doses. This was approximately the same mean value seen in the group as a total. The mean lung deposition was lower, 12%, at 4.5 μg in these patients. This is most probably due to urine concentration values below the LLOQ and thereby an underestimation of lung deposition.

The mean lung deposition of formoterol inhaled via Turbuhaler by the COPD patients in the present study was 24% of the nominal dose, with a 95% C.I. between 21% and 26%. This value is close to the value obtained in a study of healthy subjects and asthmatic patients (1) and in healthy subjects with formoterol Turbuhaler, 28% (range: 17–45%), but lower than the 49% (39–63%) reported in another study with formoterol Turbuhaler, again in healthy subjects. The present value is, however, higher than the corresponding values in asthmatic patients from two previous studies on terbutaline Turbuhaler performed with the same methodology in the same clinic.

Some physicians have argued that patients might not be able to produce a high enough PIF through a DPI, such as Turbuhaler, to generate an aerosol containing a sufficient amount of fine particles in situations perceived as constrained. Actual data do not support this preconceived notion. Even so, a large majority of COPD patients were
able to generate a PIF through the Turbuhaler of more than 40 L/min during an exacerbation despite overt respiratory muscle weakness.\textsuperscript{23} In the present study, mean PIF was 59 L/min, while the lowest mean individual PIF was 45 L/min. Interestingly, the patient with the lowest PIF had a lung deposition, close to the mean deposition value. Thus, the present lung deposition value largely exceeded the 11.7% lung deposition of ipratropium bromide inhaled via a standard pMDI, in COPD patients.\textsuperscript{11}

The analysis of the more than 700 inhalations in the present study indicate that stable COPD patients with a baseline FEV\textsubscript{1} between 30% and 50% predicted are able to produce a PIF through Turbuhaler vastly exceeding 30 L/min. It should also be noted that there was no correlation between PIF and disease severity measured as baseline FEV\textsubscript{1}, nor pulmonary deposition. This indicates that a satisfactory pulmonary deposition might be expected also with a PIF below 60 L/min, a flow that was once proposed to be the target flow with Turbuhaler.\textsuperscript{24,25} Hence, the concerns about the lack of efficacy of treatments with drugs inhaled via Turbuhaler in COPD patients unable to reach an inhalation flow rate of 60 L/min,\textsuperscript{21,26} are not supported by present lung deposition data.

The current data also indicate that a reduced IV did not compromise lung deposition of formoterol in COPD patients. Actually, patients with a FEV\textsubscript{1} as low as 0.950 L (or 33% of predicted) or a FVC as low as 1.83 L (or 50% of predicted) were included in the study. Although patients with a greater FEV\textsubscript{1} or PIF generated a greater IV, when inhaling via Turbuhaler, there was no correlation between baseline FEV\textsubscript{1} and lung deposition. If anything, a trend towards a better response in FEV\textsubscript{1} and FVC for severe, as compared to moderate, COPD patients was observed.

**Pulmonary effects**

The present study demonstrated that formoterol inhaled via Turbuhaler resulted in a dose-dependent increase in mean FEV\textsubscript{1} reaching 19% of baseline with the highest, 36 \(\mu\)g dose. Likewise, mean sG\textsubscript{AW} increased by 67% with the highest dose. These improvements are in line with other studies with COPD patients, in which dose-dependent effects of formoterol on FEV\textsubscript{1} and airway resistance have been reported.\textsuperscript{27–29}

Measurements of FVC or IC reflect the degree of hyperinflation, which appear to be far more responsive to inhalation of short- and long-acting bronchodilating drugs than FEV\textsubscript{1}.\textsuperscript{17,18,30–38} Reduction of flow limitation and hyperinflation has been considered to be one of the main mechanisms through which short- and long-acting bronchodilating drugs improve exertional dyspnea and endurance in COPD.\textsuperscript{39–43} The presently reported reduction in hyperinflation after formoterol was dose-dependent, the 36 \(\mu\)g dose resulting in the most pronounced decrease. This finding provides a likely physiological explanation for the previously reported reduction of dyspnea for the 4.5, 9 and 18 \(\mu\)g doses\textsuperscript{44} and increase in exercise tolerance for the 4.5 and 9 \(\mu\)g doses.\textsuperscript{45} Whether a dose of 36 \(\mu\)g may further enhance long-term exercise tolerance or reduce sensation of dyspnea is not unlikely, since both our study and that of Cazzola et al. unequivocally demonstrated that the effects on pulmonary function of 36 \(\mu\)g formoterol inhaled via Turbuhaler exceeded those of the 18 \(\mu\)g dose.\textsuperscript{27} It thus appears that the "maximum" and the "optimal" dose might exceed the currently recommended dose of 18 \(\mu\)g for maintenance treatment of COPD. Apparently, the 36 \(\mu\)g dose was very well tolerated as a single dose in the present study, as were doses up to 90 \(\mu\)g of inhaled formoterol in another series of patients with COPD.\textsuperscript{46}

We did not only make estimations of regression parameters of nominal-dose/response relationships, but also of lung-dose/response relationships, hypothesizing that lung-dose could be used as a sharper surrogate marker for the effects of inhaled formoterol in COPD. In fact, lung-dose was a better predictor of functional improvement than nominal-dose for FEV\textsubscript{1}, FVC, IC, and sG\textsubscript{AW}, since the confidence intervals were tighter for the lung-dose/relationship than for the nominal-dose/response relationship. The present investigations thus indicate that lung deposition is of clinical relevance in COPD, just as in asthma.\textsuperscript{2}

**Conclusion**

It can be concluded that moderate as well as severe COPD patients manage to inhale formoterol properly via Turbuhaler. In the 4.5–36 \(\mu\)g dose range, lung deposition is about 24% both in moderate and severe COPD, and results in a dose–response for FEV\textsubscript{1}, FVC, IC, and sG\textsubscript{AW}. More importantly, a sharper dose–response relationship could be shown between lung-dose of inhaled formoterol and effects on pulmonary function. This study suggests that lung deposition could serve as a surrogate for clinical effects and assessment of bioequivalence of different formulations containing the same bronchodilating drug.

**Conflict of interest**

Eric Derom received $1950 in 2002; $2280 in 2003 and $2495 in 2004 serving on an advisory board for GlaxoSmithKline; he received $106,930 for the period 2003–2005 from Altana Pharma, $5890 for the period 2003–2005 from GlaxoSmithKline, $100,280 in 2004 from SGSBiopharma and $163,400 in 2003 from Novartis as research grants for participating in clinical trials; he received a grant from AstraZeneca to allow him to attend the ATS 2004 and from Altana Pharma to attend the ERS 2005 Congress.

Kerstin Strandgården is employed at AstraZeneca, Lund since 1999.

Vanessa Schelfhout has no conflict of interest.

Lars Borgström is employed at AstraZeneca, Lund since 1983.

**Acknowledgments**

It is a pleasure to acknowledge Vera Collart for excellent technical assistance, Vivian Kristofferson for study coordination, and Thomas Bengtsson for statistical evaluations.
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