The course of inhalation profiles during an exacerbation of obstructive lung disease

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Summary Background: Acute exacerbations of asthma and chronic obstructive pulmonary disease (COPD) are associated with increased airflow limitation, hyperinflation and respiratory muscle fatigue. It is unclear, whether patients are able to perform adequate inhalations through various inhalation devices with different orifices during an exacerbation.

The aim of this study was to examine the evolution of inhalation profiles of patients inhaling through Diskus, Turbuhaler, pressurized metered dose inhaler (pMDI) and Volumatic and consequently the appropriateness of using the various devices during an exacerbation.

Measurements: 15 hospitalized patients participated in this randomized comparison of inhalation profiles through the four placebo-devices. For each device, triplicate inhalation profiles were recorded during day 1–9 of admission and in stable phase (day 50).

Results: The mean percentage of patients performing optimum inhalation profiles was 100% for Diskus, 60% for Turbuhaler, 14% for pMDI and 87% for Volumatic over the interval of day 1–9 and day 50. Patients with an inspiratory muscle strength (MIP) of less than 6 kPa were generally unable to generate the optimum flow through the Turbuhaler (>60 l/min).

Conclusion: The Diskus and Volumatic can be used effectively in the acute phase of an exacerbation of asthma or COPD. The Turbuhaler could be optimally used after the fifth day of convalescence. The pMDI is rather unsuitable during an exacerbation.

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Introduction

An acute exacerbation of obstructive lung disease (e.g. asthma and chronic obstructive pulmonary disease (COPD)) can be elicited by various agents, and is associated with considerable symptomatic burden and pathophysiological changes...
and, depending on its severity, a common reason for hospital admission.1–3

Inhalation therapy with bronchodilators and/or corticosteroids is the mainstay of the treatment both in stable disease and during an exacerbation. During an exacerbation the airway caliber and the level of hyperinflation changes. Furthermore, the patients use additional systemic corticosteroids that may cause myopathy, which in turn, may have consequences for the patients’ performance using the various inhalation devices. The use of a pressurized metered dose inhaler (pMDI) has some potential drawbacks, such as the required hand–lung co-ordination. These drawbacks are undesirable, especially in the acute situation.

The use of dry powder inhalers (DPI) during an exacerbation may be hampered by decreased respiratory muscle strength due to hypoxia, hypercapnia, hyperinflation and use of corticosteroids.4 Therefore, it is still unclear whether the DPIs could be effective in the acute phase of an exacerbation. Furthermore, the various devices have different orifices and thus different resistivities (resistance to airflow). One may question, whether patients will be able to perform adequate inhalations through high-resistivity devices during an exacerbation. Should devices be changed during an exacerbation? The aim of this study was to measure the evolution of the inhalation profiles using placebo Diskus, Turbuhaler, pMDI and pMDI plus Volumatic (pMDI V) in order to evaluate whether one or more devices are less suitable to be used during an exacerbation.

Asthma and COPD patients performed the inhalation profiles during the acute phase of an exacerbation (the day after admission), the phase of convalescence (day 5 of admission) and in stable phase (6 weeks after discharge). The second aim was to investigate whether one or more patient characteristics (age, various lung function variables, inspiratory muscle strength) could predict the ability of the patient to use a certain device during an exacerbation.

Methods

Study population

Fifteen patients with obstructive pulmonary disease (five asthmatics and 10 COPD patients; 10 male, mean age 61.4 (11.1) years) admitted for an acute exacerbation5 participated in the study (Table 1). Ten patients were ex-smoker; three of them were still smoking. All of them received bronchodilators by nebulizer, oral or intravenous steroids and theophylline. Before the exacerbation, they used pMDI plus spacer (seven patients), DPI (four patients) and six patients used pMDI alone. Exclusion criteria were other pulmonary diseases (e.g. pneumonia, tuberculosis), a history of thoracic surgery and inadequacy to understand instructions. The hospital ethics committee approved the study and the participants signed a consent form.

Exacerbations of asthma and COPD were defined according to previously described criteria.5,6

Study design

The study was performed as an open randomized comparison of the inhalation profiles performed by hospitalized patients using a placebo Turbuhaler®, Diskus®, pMDI and pMDI V®.

Patients were given specific additional verbal and written instructions, according to instructions on the manufacturers’ leaflet. They inhaled three times through each placebo device, in an random order. The first measurement started between 12 and 24 h after admission (day 1). Measurements were done at day 1, 2, 3, 4, 5, 6, 7, 8 and 9 (not during the weekends). Measurements were also made in a clinically stable condition 6 weeks after discharge from the hospital (day 50). Each measurement was performed at the same time of the day, within 3 h after maximal bronchodilation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Day 1 (exacerbation)</th>
<th>Day 50 (stable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1%pr</td>
<td>48.2 (24.7)</td>
<td>59.7 (31.9)*</td>
</tr>
<tr>
<td>FEV1(l)</td>
<td>1.4 (0.8)</td>
<td>1.8 (1.0)*</td>
</tr>
<tr>
<td>FEV1/VC (%)</td>
<td>44.9 (17.2)</td>
<td>48.6 (21.5)</td>
</tr>
<tr>
<td>IC (l)</td>
<td>2.0 (0.8)</td>
<td>2.7 (0.8)*</td>
</tr>
<tr>
<td>MEF50 (l/s)</td>
<td>0.9 (0.7)</td>
<td>1.6 (1.5)*</td>
</tr>
<tr>
<td>FIV1 (l)</td>
<td>2.2 (1.1)</td>
<td>3.0 (1.0)*</td>
</tr>
<tr>
<td>PIF (l/s)</td>
<td>3.3 (1.7)</td>
<td>4.7 (2.0)*</td>
</tr>
<tr>
<td>pH</td>
<td>7.42 (0.004)</td>
<td>Not tested</td>
</tr>
<tr>
<td>pO2 (kPa)</td>
<td>8.3 (0.97)</td>
<td>Not tested</td>
</tr>
<tr>
<td>pCO2 (kPa)</td>
<td>5.7 (1.3)</td>
<td>Not tested</td>
</tr>
<tr>
<td>MIP%pr</td>
<td>62.1 (31.8)</td>
<td>95.7 (32.2)*</td>
</tr>
<tr>
<td>MEP%pr</td>
<td>53.1 (22.2)</td>
<td>75.5 (25.0)*</td>
</tr>
<tr>
<td>Rs6 (cm H2O l/s)</td>
<td>4.3 (1.0)</td>
<td>4.0 (1.5)</td>
</tr>
</tbody>
</table>

FEV1%pr: forced expiratory volume in 1 s as percentage of predicted; FEV1: forced expiratory volume in 1 s; PIF: peak inspiratory flow; FIV1: forced inspiratory volume in 1 s; FEV1/VC: FEV1/vital capacity; IC: inspiratory capacity; MIP%pr and MEP%pr: maximal in- and expiratory mouth pressure as percentage of predicted; Rs6: airway resistance at 6 Hz; Data given are mean (sd).

*P<0.05 as compared to day 1.
Measurements

A flow-volume curve was taken with an integrating pneumotachograph (Spiro Analyzer SensorMedics, Bilthoven, The Netherlands). Maximal in- and expiratory mouth pressure (MIP and MEP) were measured as described by Wilson et al. with a micro-mouth pressure meter (Micro Medical Ltd., UK). Airway resistance (Rrs) was measured with Forced Oscillation Technique (Random Noise Oscillator, SensorMedics, Bilthoven, The Netherlands).

Inhalation profile

The inhalation profiles of the DPIs were recorded by a pressure transducer (GlaxoSmithKline R&D Department, Ware, UK), measuring pressures in the mouthpiece, during inhalation through Diskus and Turbuhaler. The inhalation profiles were stored into the inhalation profile recorder.

The variables of the DPI-inhalation profile recorder are peak inspiratory flow (PIF) (l/min); inhaled volume (Vi) (l) and inhalation time (Ti) (s).

The inhalation profiles of the pMDI and pMDI_V were recorded with a pMDI placed in a pressure-measuring manifold. The variables of this recorder are PIF (l/min); Vi (l); Ti (s) and actuation time (time between the start of the inhalation and the activation of the canister) (Ta) (s). The variables of the Volumatic inhalation profiles are actuation time (Ta)(s) and number of inhalations during the recorded time.

Optimum use

Previous in vitro studies showed that Diskus operates effectively at PIF_diskus > 30 l/min. Optimum Diskus-use was defined as inhalations with PIF_diskus > 30 l/min. The Turbuhaler produces a therapeutic dose at PIF > 30 l/min. However, for the Turbuhaler, a maximum fine particle mass and consistent dose delivery has been described at PIF > 60 l/min. So, for this study, a PIF_turbuhaler > 30 l/min is considered 'minimal' and PIF_turbuhaler > 60 l/min as being 'optimal'.

For the use of a pMDI, an actuation at the start of a slow inhalation is essential. The recommended flow for the pMDI is between 25 and 90 l/min. So, the optimum pMDI-use was defined as 0 ≤ Ta ≤ 0.2 s and 25 < PIF_pMDI < 90 l/min.

We defined optimum Volumatic-use when a separate puff was inhaled in four tidal breaths within 20 s, starting between −4 and 0.5 s after actuation.

Statistical analysis

SPSS for Windows version 9.0 and the SAS system for Windows version 6.12 were used for the statistical analysis.

Patient characteristics of days 1, 5 and 50 were compared using the Wilcoxon-matched paired signed rank test.

The incidences of optimum inhaler use were calculated. For this analysis the last observation carried forward method was used to input occasional missing data.

For the evaluation of the various variables, repeated measurements analysis of variance using SAS PROC MIXED was used. This statistical program was also used to evaluate the relationship between lung function variables and inhalation profiles, while taking inter- and intra individual differences into account using random-coefficients models. Data are expressed as mean ± SEM or as otherwise indicated. A two-sided P-value of 0.05 was considered the limit of significance.

Results

All patients completed at least six measurements during admission. Two of the 15 patients did not complete the measurement 6 weeks after discharge.

Incidences of optimum inhalation profiles

We determined which recorded inhalation profiles could be considered optimal. The incidences (percentages) of optimum profiles are shown in Fig. 1.

Diskus

All Diskus inhalations were optimally performed with PIF > 30 l/min.

Turbuhaler

All patients were able to generate the minimal PIF_turbuhaler > 30 l/min. Forty percent of the inhalations through the Turbuhaler were performed with sub-optimal PIF_turbuhaler < 60 l/min during the exacerbation (day 1–9). There was no significant difference of the percentage of optimum Turbuhaler inhalations (> 60 l/min), between the inhalations performed during the exacerbation period (day 1–9) and inhalations performed in the stable phase (day 50) (60 vs. 64%). So, six (one asthmatic) of the 15 patients performed all inhalations during day 1–9 with PIF_turbuhaler < 60 l/min. Four of them also inhaled in stable phase with PIF_turbuhaler < 60 l/
min. The two others had dropped out of the study. Two patients inhaled only on day 1 with PIF_{turbuhaler} < 60 l/min, one asthma patient was unable to generate the optimum flow, up to day 5.

**pMDI**
The recommended flow for the pMDI is 25 < PIF < 90 l/min and the optimum actuation time is between 0.0 and 0.2 s after the start of the inhalation. Fig. 1 shows that in 14% of the inhalations both components were correctly performed. In 56% of the pMDI inhalations, the hand-lung co-ordination was inadequate and 66% were performed with a too high flow (mean (SD) PIF_{pMDI} = 107.7 (31.7) l/min).

**pMDI plus Volumatic**
Eighty-seven percent of the Volumatic inhalations were optimally performed.

![Figure 1](image)

**Figure 1** Incidences of optimum inhalation characteristics. Diskus: PIF > 30 l/min; Turbuhaler; PIF > 60 l/min; pMDI: 25 < PIF < 90 l/min and actuation time (T_0) 0.0 < T_0 < 0.2 s; Volumatic: 4 < T_0 < 0.5 s and four inhalations/20 s. The values under the legend were the means of optimum inhalation profiles over the whole observation period. The means of the optimum inhalation profiles over the study period were for Diskus, Turbuhaler, pMDI and Volumatic, respectively, 100%, 60%, 14% and 87%.

### Evolution of inhalation profile variables

Table 2 shows the PIF of Diskus and Turbuhaler during the course of an exacerbation. The mean PIF values during exacerbation were compared to the values on day 50. PIF_{diskus} and PIF_{turbuhaler} on day 1 were significantly lower compared to the PIF values on day 5 and day 50. No significant differences were found between the PIF values on day 5 and day 50 for both Diskus and Turbuhaler.

<table>
<thead>
<tr>
<th></th>
<th>Day.1 (acute phase)</th>
<th>Day.5 (phase of convalescence)</th>
<th>Day.50 (stable phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIF_{diskus} (l/min)</td>
<td>86 (6.6) [44–131]</td>
<td>95 (7.9) [49–140]^*</td>
<td>101 (7.6) [51–134]^*</td>
</tr>
<tr>
<td>PIF_{turbuhaler} (l/min)</td>
<td>59 (4.7) [33–88]</td>
<td>67 (5.0) [34–96]^*</td>
<td>72 (5.2) [39–93]^*</td>
</tr>
</tbody>
</table>

*Data are expressed as mean (SEM) [range].

*P < 0.05 as compared to Day.1.*

### Effects of lung function variables on PIF

The effects of lung function variables on PIF were evaluated by the repeated measurement ANOVA (SAS proc. mixed). MIP and MEF_{50} were found to be the most significant predictors for PIF_{diskus}. There was an average increase of 5.0 (0.8) l/min of PIF_{diskus} per kPa MIP increase (P < 0.001). The average increase of PIF_{diskus} per unit MEF_{50} was 7.3 (2.1) (P < 0.001). MIP and inspiratory capacity (IC) were found to be the most significant predictors for PIF_{turbuhaler}. There was an average increase of 4.3 (0.6) l/min of PIF_{turbuhaler} per kPa MIP increase (P < 0.001). The average increase of PIF_{turbuhaler} per liter IC was 8.6 (7.5) l/min (P < 0.001). Data are expressed as mean (SEM).

### Discussion

Four different inhalation devices were studied in hospitalized asthma and COPD patients during a severe exacerbation. The patient characteristics showed decreased lung function and respiratory muscle strength variables during the exacerbation. The aim of this study was to observe the ability of the patients to use different inhalers and the evolution of the inhalation profiles through the four inhalation devices. Furthermore, patient characteristics predicting optimal use of the devices were described.
Incidence of optimum inhalation profiles

(i) All Diskus inhalations were performed at all times with more than the minimum recommended flow of 30 l/min.
(ii) Turbuhaler: All inhalations were performed above the minimum flow (>30 l/min). So, all patients should be able to inhale a therapeutic dose. However, 40% of the inhalations of the Turbuhaler during the exacerbation period (day 1–9) were performed with the sub-optimum flow (<60 l/min). Nine (of 15) patients failed to generate this flow on day 1. This could be due to decreased respiratory muscle function since hyperinflated patients (IC 2.0 (0.8) l and patients with decreased MIP-values (MIP%pr 62.1) were included in our study. Fig. 2 shows that, patients who performed MIP less than 6 kPa, were unable to generate PIFturbuhaler >60 l/min.

Brown et al.18 measured PIFturbuhaler in 99 acute asthma patients (aged 42 years, range 11–88) within 30 min of admission. They found mean PIFturbuhaler of 60 l/min. This was similar to our PIFturbuhaler, day 1 (59 l/min), although we measured older patients in the acute stage.

Dewar et al.19 showed in 100 (stable and acute) COPD patients that all patients were able to perform PIFturbuhaler of 28 l/min and 83% were able to generate PIFturbuhaler >40 l/min. These data were also similar to our results: Fig. 2 shows that approximately 90% of the Turbuhaler-inhalations were performed with >40 l/min. It has been shown that recovery of lung function variables to baseline was incomplete in 7.1% of COPD-patients at 91 days after the start of an exacerbation. Therefore, we have to assume that a small part of our patients were not in ‘stable condition’ 6 weeks after discharge. However, after day 5 of the exacerbation, the percentage of patients being able to generate optimal flows for the various devices did not differ from the stable period.
(iii) In 56% of the pMDI inhalations, the hand–lung co-ordination was inadequate and 66% were performed with a too high flow. In only 14% of pMDI-inhalations both, major relevant components of pMDI-use, were carried out correctly. Poor pMDI-inhalation technique is well documented: the frequency of misuse ranges from 14% to 90%.3,21–23 Fifty-four percent of our patients were pMDI-naive. Another factor that could be attributed to the bad performance was the age of our patients. Our patients were middle-aged. Some studies showed that elderly patients are consistently poor performers.24,25
(iv) Volumatic: Eighty-seven percent of the Volumatic inhalations were optimally performed. Our findings were in accordance with several other studies showing the usefulness of pMDI plus spacer in the acute exacerbation.26–28

Evolution of inhalation profile variables

We compared the PIFs of Diskus and Turbuhaler. For Diskus it was shown that the PIFday 1 was significantly lower compared to the values on day 5 and day 50. However, we do not expect that this is of clinical relevance, because all patients generated more than the minimum recommended flow of 30 l/min. We found also a decreased PIFturbuhaler on day 1. In general, patients generated an insufficient flow during the acute phase of an exacerbation. Before prescribing the Turbuhaler, one must check the actual inspiratory flow through a Turbuhaler using a PIF-meter, with a device specific resistivity (e.g. in Check Dial, Clement Clarke Int. Ltd. UK) or patient’s MIP values should exceed 6 kPa.

Effects of lung function variables on PIF

The highest significant correlations were found between MIP and MEF50 and PIFdiskus. The most significant predictors of PIFturbuhaler were MIP and IC. These findings confirmed that the ability of patients to inhale through a DPI depends on their inspiratory muscle function. The generated
PIF_Turbuhaler also depends on the inspiratory capacity (a dimension of hyperinflation). Strength and endurance of the diaphragm of hyperinflated patients is impaired, because of its unfavorable position on the length tension curve. A significant correlation between MIP and IC was found (r = 0.64, P < 0.05).

Inhalation of bronchodilators by a nebulizer is the standard treatment for acute bronchial obstruction in Europe. In this study, it has been shown that Diskus and pMDI can be used effectively in the acute setting and during the phase of convalescence. It has been recommended that larger than the standard dose of bronchodilators delivered by a pMDI or DPI should be used for the treatment of patients with acute airflow obstruction. Although, there is a lack of data on optimum drug dose by hand-held inhalers, it was suggested that 1000 μg of salbutamol via pMDI plus spacer was equivalent to 2.5 mg salbutamol by nebulizer. Our patients inhaled three times through each device and no effects of fatigue were found, so five puffs of 200 μg salbutamol via Diskus or pMDI plus spacer seem to be feasible.

This study has shown the inability of patients to use a pMDI correctly in the acute phase. A pMDI should exclusively be used in combination with a spacer device, especially in the acute setting.

In conclusion, the Diskus and pMDI plus spacer can be used effectively in the acute phase of an exacerbation of asthma and COPD. Forty percent of the patients were able to inhale an optimal dose from the Turbuhaler in the acute phase, however, this device could really be optimally used after day 5. Decreased respiratory muscle function predicts a sub-optimal use of the Turbuhaler. The pMDI is rather unsuitable without a spacer, especially during an exacerbation.

References


