Differences in Adherence to Common Inhaled Medications in COPD

Kirsten Koehorst-ter Huurne, Kris Movig, Paul van der Valk, Job van der Palen & Marjolein Brusse-Keizer

To cite this article: Kirsten Koehorst-ter Huurne, Kris Movig, Paul van der Valk, Job van der Palen & Marjolein Brusse-Keizer (2015): Differences in Adherence to Common Inhaled Medications in COPD, COPD: Journal of Chronic Obstructive Pulmonary Disease, DOI: 10.3109/15412555.2014.995292

To link to this article: http://dx.doi.org/10.3109/15412555.2014.995292

Published online: 16 Mar 2015.
Differences in Adherence to Common Inhaled Medications in COPD

Kirsten Koehorst-ter Huurne, Kris Movig, Paul van der Valk, Job van der Palen, and Marjolein Brusse-Keizer

Abstract

Objective: To study differences in adherence to common inhaled medications in COPD.

Methods: Adherence of 795 patients was recorded from pharmacy records over 3 years in the COMIC cohort. It was expressed as percentage and deemed good at ≥75–≤125%, sub-optimal ≥50–<75%, and poor <50% (underuse) or >125% (overuse). Most patients used more than one medication, so we present 1379 medication periods.

Results: The percentages of patients with good therapy adherence ranged from 43.2 (beclomethasone) – 75.8% (tiotropium); suboptimal from 2.3 (budesonide) – 23.3% (fluticasone); underuse from 4.4 (formoterol/budesonide) – 18.2% (beclomethasone); and overuse from 5.1 (salmeterol) – 38.6% (budesonide). Patients using fluticasone or salmeterol/fluticasone have a 2.3 and 2.0-fold increased risk of suboptimal versus good adherence compared to tiotropium. Patients using salmeterol/fluticasone or beclomethasone have a 2.3- and 4.6-fold increased risk of underuse versus good adherence compared to tiotropium. Patients using budesonide, salmeterol/fluticasone, formoterol/budesonide, ciclesonide and beclomethasone have an increased risk of overuse versus good adherence compared to tiotropium. Adherence to inhalation medication is inversely related to lung function.

Conclusion: Therapy adherence to inhalation medication for the treatment of COPD is in our study related to the medication prescribed. Tiotropium showed the highest percentage of patients with good adherence, followed by ciclesonide, both dosed once daily. The idea of improving adherence by using combined preparations cannot be confirmed in this study. Further research is needed to investigate the possibilities of improving adherence by changing inhalation medication.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality throughout the world. In general, the treatment of COPD is supportive, aimed at relieving patients symptoms, to decrease the number of exacerbations, and to improve quality of life (1). Bronchodilators are the key element in pharmacological management of COPD (1). In addition, since pulmonary inflammation is prominent in COPD (2), anti-inflammatory drugs such as inhaled corticosteroids are often used.

The effectiveness of inhaled medications is strongly influenced by the patient’s drug adherence. Adherence to medication has been shown to be associated with reduced risk of death and hospitalization (3).

Medication adherence is influenced by patient and medication related factors. Critical patient related factors for optimal medication adherence in patients with COPD are patients’ disease and treatment acceptance,
knowledge about and faith in the treatment, effective patient-clinician relationship, and routinisation of drugtherapy (4–6). Medication related factors such as frequent daily use and multiple dosing have both shown to have a negative influence on adherence (7). Patients with COPD often use a medication regimen requiring multiple daily dosages during a prolonged period and often use different medications simultaneously. All these factors combined can make therapy adherence for COPD patients a difficult task.

Nonadherence to inhalation medication can be divided in several categories. The use of medication has to start with obtaining the medication. After obtaining the patient can underuse, overuse or show improper use (for example forgetfulness and alteration of schedules and doses) of the medication (4,8).

A specific problem with inhalation medication is the use of the device in which the medication is administered. Improving inhalation technique can improve adherence (9).

Medication adherence with regard to maintenance medication in patients with COPD is generally poor, varying in medication database studies from 28–40% for inhalation corticosteroids, 29–35% for corticosteroid/sympathicomimetic combinations and 54–61% for long-acting sympathicomimetics and tiotropium (10–12).

Many adherence studies use data of one-year follow-up and cannot discriminate between asthma and COPD patients (11,13,14). Medication use in COPD is long term. We therefore conducted a study to investigate therapy adherence with inhalation medication over a period of 3 years in a well-defined cohort of confirmed COPD-patients to give an estimate on long-term use.

Methods

Setting and design

This study is part of the Cohort of Mortality and Inflammation in COPD (COMIC) study a single-centre prospective cohort study. From December 2005 until April 2010, 795 patients were included with a follow-up period of 3 years. Patients were recruited at the outpatient clinic of the Department of Pulmonology, Medisch Spectrum Twente Hospital, Enschede, located in the Eastern part of The Netherlands, serving a catchment population of approximately 264,000 persons. The study was approved by the hospital’s Medical Ethical Committee (P05–49). All patients provided written informed consent.

To be eligible for the study patients had to meet the following criteria: (1) a clinical diagnosis of COPD, as defined by the GOLD criteria (2) current or ex-smoker; (3) age 40 years or over; (4) no medical condition compromising survival within the follow-up period or serious psychiatric morbidity, and (5) absence of any other active lung disease (eg, sarcoidosis), (6) no maintenance therapy with antibiotics, (7) and the ability to speak Dutch. Patients were consecutively enrolled when hospitalised for an acute exacerbation of COPD (AECOPD group) or when visiting the outpatient clinic in stable state (stable state group).

To be included in the AECOPD group, patients had to be hospitalised for an AECOPD and be able to produce an adequate sputum sample at the day of hospitalisation. To be included in the stable state group patients had to meet the following criteria: no use of antibiotic and/or prednisolone 4 weeks prior to enrolment and no exacerbation less than 4 weeks before study entry. Of the 1503 patients that were screened for eligibility, a total of 795 were included. All surviving patients completed the three-year follow-up period. All patients were treated according to standard care. Demographic data was collected from medical records.

Lung function and smoking status were both determined at baseline. Lung function was measured by spirometry, performed according to standardised guidelines (15). Forced Expiratory Volume in 1 sec (FEV₁) and Vital Capacity (VC) were measured until three reproducible recordings (less than 5% difference) were obtained. Smoking status was determined by the Vlagtwedde questionnaire (16).

The primary outcome, therapy adherence, was recorded from patients’ pharmacy records. The patients were not aware that their medication records were going to be used for the monitoring of therapy adherence. Theoretical duration of exposure was calculated using information on dispensing date, total supply, and dosage regimen. We computed the total number of days for which patients had collected medication during follow-up and divided this by the total number of days between the first and last medication collection during follow up plus the day’s supply of the last refill (17).

This was expressed as a percentage and adherence was deemed good if it was ≥75–≤125%, sub-optimal between ≥50–<75%, and poor below <50% (underuse) or above >125% (overuse). In literature there is no consensus on acceptable therapy adherence, definitions vary from >70% to >80% for a clinical research setting. We decided to set the limit for optimal adherence at ≥75, which is between these two definitions. Next to this, we decided to choose an upper cut-off point as well for optimal adherence (>125%), in order to exclude overuse from this category (3,10,11,18). We excluded medication when it was prescribed once only or was used less than 90 days.

Computerized pharmacy data made it feasible to monitor medication adherence by tracking requests for refills. Computerized drug dispensing histories from Dutch pharmacies are virtually complete and include data concerning the dispensed drug, the prescriber, the dispensing date, the amount dispensed, the prescribed dose regimens, and the estimated duration of use. In The Netherlands, there is a strong pharmacy-patient liaison for reimbursement of prescription drugs, a high degree of computerization, the use of standardized classification and coding systems, and a strong commitment of pharmacists to surveillance of medication.
The following bronchodilators were used: salmeterol and tiotropium. Furthermore, the inhaled corticosteroids beclomethasone, ciclesonide, fluticasone and budesonide and the combined preparations of fluticasone/salmeterol and budesonide/formoterol were included in the analyses. Therapy adherence with formoterol was not analysed, because formoterol (unlike salmeterol) can be used on demand as well and this confounds our calculation of adherence (19).

Statistical analyses
Baseline characteristics are reported as mean with SD for continuous variables, or as numbers with corresponding percentages for categorical or dichotomous variables. Not normally distributed continuous variables are reported as median with corresponding interquartile range (IQR).

We investigated the relationship between therapy adherence and type of medication with Nominal Regression analyses. Tiotropium and good therapy adherence were set as reference in the Nominal Regression analyses.

Furthermore potential confounders (age, sex, smoking status, lung function) were first tested for their association with therapy adherence. Associated variables were subsequently tested for their association with type of medication. For categorical variables this association was tested by means of Chi-square tests or Fisher exact tests, as appropriate. For continuous variables this association was tested with an ANOVA or Kruskal–Wallis test as appropriate.

Variables that were both associated with therapy adherence and type of medication were all entered in the multivariate Nominal Regression analyses. Subsequently, potentially confounding variables with the highest p-value were eliminated from the model one by one until the fit of the model decreased significantly, based on the –2 Log Likelihood.

All statistical calculations were carried out with the SPSS statistical package (version 21.0) and p-values <0.05 were considered significant.

Results
The study population included 795 patients (Table 1). Patients were predominantly male (61.1%). The mean age of the study population was 68 years. Almost three-quarters of the patients were ex-smokers.

Table 2 displays the number (%) of patients in the subgroups of therapy adherence for the different inhalation medications. Because many patients used more than one type of inhaled medication and since use of one medication in different devices (for example MDI and Diskus) was scored separately during the observation period, data on 1379 periods of medication use are presented. The majority of the study patients were treated with tiotropium and salmeterol/fluticasone.

The percentages of patients with good therapy adherence within the studied medications ranged from 43.2 (beclomethasone) – 75.8% (tiotropium); suboptimal adherence ranged from 2.3 (budesonide) – 23.3% (fluticasone); underuse from 0 (ciclesonide) – 18.2% (beclomethasone); and overuse from 5.1 (salmeterol) – 38.6% (budesonide). All inhaled medications had a median time of use of more than 25 months except beclomethasone (15) and ciclesonide (23.5). The Chi-square test showed an association between therapy adherence and the studied medications (p < 0.001).

To compare the four categories of therapy adherence between inhalation medications we used Nominal Regression analyses. Because the highest percentage of patients with good adherence was observed for tiotropium, this medication, including good therapy adherence was set as reference in Table 3.

Of the potential confounders listed in Table 1, FEV1 in litres, FEV1 % predicted and FEV1/VC ratio were both associated with type of medication as well as with therapy adherence and were therefore potential confounders that should be entered to the multivariate Nominal Regression analyses. Due to multicollinearity between FEV1 in litres, FEV1 % predicted and FEV1/VC ratio, only the variable with the best model fit was entered to multivariate Nominal Regression analyses, which was FEV1 in litres.

Compared to tiotropium, patients using fluticasone or salmeterol/fluticasone had a 2.3- and 2.0-fold increased risk of suboptimal versus good adherence (Table 3). Patients using salmeterol/fluticasone or beclomethasone had a 2.3- and 4.6-fold increased risk of underuse versus good adherence. Patients using budesonide, beclomethasone, formoterol/budesonide,
ciclesonide and salmeterol/fluticasone, beclomethasone had an increased risk of overuse versus good adherence.

Compared to fluticasone as reference medication, budesonide had a 0.12 fold risk of suboptimal use compared to optimal use; budesonide, formoterol/budesonide and beclomethasone had an increased risk of overuse (6.1, 3.1 and 4.8, respectively) compared to optimal use, and beclomethasone had a 4.3-fold increased risk of underuse.

FEV$_1$(L) at baseline was related to poor adherence, both underuse and overuse.

Underuse was associated with a higher FEV$_1$ at baseline compared to good adherence, while overuse was associated with a lower FEV$_1$ at baseline compared to good adherence.

**Discussion**

Therapy adherence to inhalation medication for the treatment of COPD is in our study related to the medication prescribed. The medications dosed once daily, tiotropium and ciclesonide, showed the highest percentage of patients with good adherence. Medication dosed one time daily is a known factor that improves adherence. Adherence declines as the number of daily doses increased (20).

The percentage of patients with good adherence with tiotropium is high (76%) compared to literature. Ismaila et al. found that 61.1% and 62.9% of the tiotropium users showed good adherence (12). Also for corticosteroids and corticosteroids combined with adrenergics high percentages of good adherence were observed in our study (varying between 59 and 68%). Krigsman et al. found that only 28 and 29% of the patients showed good adherence for corticosteroids and corticosteroids combined with adrenergics (11). Vestbo et al. found that 79.8% of the patient showed good adherence with salmeterol, fluticasone propionate or a combination of these two over a study period of 3 years. However, these patients were aware that their therapy adherence was being monitored and they had to bring all inhalers at every visit to exchange them for new ones (3).

All three studies used 80% as cut-off point for good adherence. Changing the cut-off in our study to 80% did not influence the “good” adherence levels (data not shown). Just as Krigsman did, we decided to choose an upper cut-off point as well, in order to study overuse, another form of therapy nonadherence.

Therapy adherence in a clinical trial setting is usually higher because patients are motivated by the clinical setting. In the COMIC study patients were not aware that their medication records were going to be used for the monitoring of therapy adherence. We therefore do

### Table 2. Number (%) of patients in the subgroups of therapy adherence per medication

<table>
<thead>
<tr>
<th>Medication</th>
<th>Good ≥75–≤125%</th>
<th>Suboptimal ≥50–&lt;75%</th>
<th>Underuse &lt;50%</th>
<th>Overuse &gt;125%</th>
<th>Months used median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiotropium (n=566)</td>
<td>429 (75.8)</td>
<td>68 (12.0)</td>
<td>36 (6.4)</td>
<td>33 (5.8)</td>
<td>28.7 (15.1–35.5)</td>
</tr>
<tr>
<td>Ciclesonide (n=22)</td>
<td>15 (68.2)</td>
<td>3 (13.6)</td>
<td>0</td>
<td>4 (18.2)</td>
<td>23.5 (15.8–35.5)</td>
</tr>
<tr>
<td>Salmeterol (n=39)</td>
<td>26 (66.7)</td>
<td>6 (15.4)</td>
<td>5 (12.8)</td>
<td>2 (5.1)</td>
<td>27.1 (6.9–35.2)</td>
</tr>
<tr>
<td>Fluticasone (n=73)</td>
<td>46 (63.0)</td>
<td>17 (23.3)</td>
<td>4 (5.5)</td>
<td>6 (8.2)</td>
<td>25.7 (12.5–34.9)</td>
</tr>
<tr>
<td>Formoterol/Budesonide (n=91)</td>
<td>56 (61.5)</td>
<td>12 (13.2)</td>
<td>4 (4.4)</td>
<td>19 (20.9)</td>
<td>31.2 (15.9–36.5)</td>
</tr>
<tr>
<td>Salmeterol/Fluticasone (n=500)</td>
<td>295 (59.0)</td>
<td>95 (19.0)</td>
<td>55 (11.0)</td>
<td>55 (11.0)</td>
<td>27.5 (13.7–35.0)</td>
</tr>
<tr>
<td>Budesonide (n=44)</td>
<td>23 (52.3)</td>
<td>1 (2.3)</td>
<td>3 (6.8)</td>
<td>17 (38.6)</td>
<td>28.2 (17.4–36.7)</td>
</tr>
<tr>
<td>Beclomethasone (n=44)</td>
<td>19 (43.2)</td>
<td>7 (15.9)</td>
<td>8 (18.2)</td>
<td>10 (22.7)</td>
<td>15.7 (7.5–31.7)</td>
</tr>
</tbody>
</table>

### Table 3. Nominal regression analyses of medication vs. therapy adherence

<table>
<thead>
<tr>
<th>Medication</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suboptimal (≥50–&lt;75%) (n=209)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV$_1$(L) baseline</td>
<td>1.1</td>
<td>0.8–1.4</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>1.3</td>
<td>0.4–4.4</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>1.4</td>
<td>0.6–3.6</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>2.3</td>
<td>1.3–4.3</td>
</tr>
<tr>
<td>Formoterol/Budesonide</td>
<td>1.4</td>
<td>0.7–2.7</td>
</tr>
<tr>
<td>Salmeterol/Fluticasone</td>
<td>2.0</td>
<td>1.4–2.9</td>
</tr>
<tr>
<td>Budesonide</td>
<td>0.3</td>
<td>0.04–2.1</td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>2.3</td>
<td>0.9–5.7</td>
</tr>
<tr>
<td>Underuse (&lt;50%) (n=115)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV$_1$(L) baseline</td>
<td>1.5</td>
<td>1.1–2.1</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>2.1</td>
<td>0.8–5.9</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>1.1</td>
<td>0.4–3.2</td>
</tr>
<tr>
<td>Formoterol/Budesonide</td>
<td>0.8</td>
<td>0.3–2.4</td>
</tr>
<tr>
<td>Salmeterol/Fluticasone</td>
<td>2.3</td>
<td>1.5–3.6</td>
</tr>
<tr>
<td>Budesonide</td>
<td>1.6</td>
<td>0.4–5.5</td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>4.6</td>
<td>1.9–11.3</td>
</tr>
<tr>
<td>Overuse (&gt;125%) (n=145)***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV$_1$(L) baseline</td>
<td>0.6</td>
<td>0.4–0.8</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>3.6</td>
<td>1.1–11.6</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>0.5</td>
<td>0.1–4.1</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>1.6</td>
<td>0.6–4.0</td>
</tr>
<tr>
<td>Formoterol/Budesonide</td>
<td>4.9</td>
<td>2.6–9.3</td>
</tr>
<tr>
<td>Salmeterol/Fluticasone</td>
<td>2.3</td>
<td>1.5–3.7</td>
</tr>
<tr>
<td>Budesonide</td>
<td>9.8</td>
<td>4.7–20.2</td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>7.7</td>
<td>3.3–18.1</td>
</tr>
</tbody>
</table>

*Good adherence and tiotropium were set as reference. All corrected for FEV$_1$ in Litres (L) at baseline.

**Not possible to calculate.

***One missing due to missing lung function data.
not expect a large influence on therapy adherence as observed by patients participating in a clinical trial setting. In this light the therapy adherence levels found in our study can be considered very high. This is in line with a nationwide observational study that showed higher adherence levels in our region compared to other regions in the Netherlands (21).

This study showed increased risks of suboptimal adherence, underuse and overuse for investigated inhaled corticosteroids and corticosteroid/sympathetic mimetic combinations compared to tiotropium with optimal adherence.

These differences can be caused by medication related factors as number of daily doses needed or relief of symptoms. Tiotropium relieves dyspnea whereas corticosteroids do not give immediate relief (22). The question is whether changing inhalation medication within the same class of medication can improve therapy adherence. For example if a patient shows underuse on beclomethasone would changing therapy to fluticasone improve adherence? This should be evaluated in future studies. Furthermore, could the difference in therapy adherence also be related to the device in which inhalation medication is administered?

Another interesting finding is that the idea of improving adherence by using combined preparations cannot be confirmed in this study. Differences in adherence between the inhaled corticosteroids and the combined preparations lie in the levels of over- and underuse. Adherence is significantly higher in some preparations and numerically but not statistically significant in others. Combining inhalation medication in one device is thought to improve adherence.

Yet, guidelines for the treatment of COPD (GOLD, Dutch guidelines of NHG and CBO) do not recommend the use of combined preparations to improve therapy adherence (23, 24). Our study supports this view. Given the observational design of the study it is however possible that the combined preparations were given to patients that had problems with therapy adherence on the sole preparations, thus resulting in an apparently greater rate of adherence in the remaining subjects continuing to use the sole preparations. Similar results were found for the treatment of asthma in children as well as adults (25).

Therapy adherence to inhalation medication showed to be related to FEV$_1$ at baseline. Underuse was associated with a higher FEV$_1$ at baseline, while overuse was associated with a lower FEV$_1$ at baseline. It is possible that patients with higher FEV$_1$ feel less need to use their medication and therefore show lower adherence levels. The opposite can be an explanation for overuse with a lower FEV$_1$. Turner et al found a relation between good adherence and reduced FEV$_1$. This is in line with our results (26).

There are some potential limitations in our study. Therapy adherence can be measured in several ways. Most common are the use of collected pharmacy records, questionnaires or interviews. Pharmacy records give an indication of drug refill patterns but not of the actual inhalation. Patients can decide to collect the medication to appear adherent, but can dump the medication at home (27).

Another problem with regard to the calculation of adherence is that the prescriber can change the dosage regimen without giving a new prescription. The pharmacy records do not reflect the actual use at this point. The data show the maximum levels of drug use among the patients, and it is likely that the inhaled drug volumes are lower than the volumes dispensed by the pharmacy (28,29).

We excluded medication if it was prescribed only once or for a period of less than 90 days in a period of 3 years. One time only records give no information on therapy adherence. Due to our definition a one-time prescription fill scores 100% therapy adherence. This would distort our results. We studied therapy adherence over a period of three years. Short time use defined as 90 days or less was also excluded. In the Netherlands dispensing medication for chronic use is restricted to 90 days or less. This rule was designed to reduce costs by preventing discarding large amounts of unused drugs. Patients that do not persist with new inhalation medications, a form of failing therapy adherence, were thereby excluded.

In our data a patient using one inhalation medication is registered as two separate episodes, when the inhalation medication is used in two different devices. Although a similar adherence could possibly be expected when patients use the same medication in a different inhaler, our data showed that this is often not the case (data not shown). Therefore, we decided not to combine the episodes to an overall adherence but to use the separate episodes. Next to the above mentioned limitations we were not able to investigate the effects of improving adherence by changing inhalation medication due to the observational character of the study.

Despite these limitations, major advantages of this study compared with previous published studies are the possibility to link adherence to lung function. Although other studies with pharmacy data alone lack the possibility to discriminate between asthma and COPD, our patients were all diagnosed with COPD. Many adherence studies use data of one-year follow-up. Medication use in COPD is long term. We followed our patients for 3 years, thus giving an estimate on long-term use.

**Conclusion**

Therapy adherence to inhalation medication for the treatment of COPD is related to the medication prescribed. This study also confirms that dosing a medication one time daily improves adherence and adherence to inhalation medication is related to lung function. Therefore, lung function should be taken into account when therapy adherence is assessed. The assumption that combining two inhalation medications in one device can improve therapy adherence cannot be confirmed. Further research is needed to investigate the
possibilities of improving adherence by changing inhalation medication.

Acknowledgments

The results of the current study were partly presented as a poster at the European Respiratory Society Annual Congress 2013, 7–11 September 2013.

Declaration of Interest Statement

The authors declare that there are no conflicts of interest.

This study was partly supported by an unrestricted research grant of Glaxo Smith Kline.

The authors alone are responsible for the content and writing of the paper.

References