CHARACTERIZATION OF INHALATION MANEUVERS AND PULMONARY DRUG DEPOSITION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

PhD thesis

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1. Introduction

Chronic obstructive pulmonary disease (COPD) affects more than 380 million people worldwide. The most important risk factor and the most frequent cause of COPD is tobacco smoking but several additional risk factors should be mentioned as dust, indoor air pollution from burning biomass fuels, noxious fumes and, moreover, individual genetical factors, effect of preterm birth. The symptoms of the disease include chronic cough, sputum production and shortness of breath, initially under exercise but later also at rest. These changes can lead to decrease in quality of life (QoL) and to an increased risk of infections resulting sudden worsening of symptoms – called acute exacerbations (AE).

The main diagnostic criteria of COPD are determined by lung function (LF) measurements. Dynamic parameters of expiration as forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and their ratio (FEV1/FVC) describe the most appropriate way the worsening of breathing capacity in COPD. During stable

condition or AEs inhaled agents like corticosteroids, beta2-agonists and muscarinic antagonists are the cornerstone of therapy and mostly administered via inhalation devices. Inhalers are particular devices whose mechanisms and inner structure are constructed to form a mixture of inhalative drugs, carrier molecules and air which the patient can easily inhale in order to reach a satisfying deposition at the desired locations. Four main types of inhaler devices are pressurized metered dose inhalers (pMDI), dry powder inhalers (DPI), soft mist inhalers (SMI) and nebulizers.

The effectivity of inhalation therapy can be measured through the pulmonary deposition (PD) of inhaled particles. *In vivo* measurements techniques include radioscintigraphy and pharmacokinetic methods, *in vitro* studies are mainly based on replicas of the human respiratory system. *In silico* methods provide an alternative where numerical modeling or computational fluid dynamics are able to perform thousands of drug delivery evaluations without the presence of patients or healthy volunteers.

2. Objectives

1. Comparing LF parameters measured by a hand-held spirometer using four different commercially available inhaler devices in stable and exacerbated COPD patients and healthy subjects.
2. Investigating repeatability of inhalation maneuvers using four different commercially available inhalation devices.
3. Calculating pulmonary and extrathoracic deposition based on inhalation maneuvers performed using three commercially available low-resistance inhaler devices.
4. Investigating repeatability of pulmonary and extrathoracic deposition in three commercially available inhaler devices.

3. Methods

3.1. Subjects

Patients with stable and exacerbated COPD as well as healthy volunteers were recruited to participate in our study which involved two main phases. In the first phase (Phase 1), stable (LF-COPD-S, n=16) and exacerbated (LF-COPD-AE, n=15) COPD patients took part in our study alongside healthy volunteers (LF-Controls, n=22). All COPD patients were diagnosed according to GOLD as post-bronchodilator FEV1/FVC <0.7 by a respiratory specialist. Exacerbated patients were recruited <72 hours after hospital admission due to severe AE. All patients with AE belonged to D category according to the then valid (2015) GOLD Guideline.(23) In the first phase, patients performed standard LF measurements, body plethysmography, inhalation maneuvers through commercially available inhalation devices, symptoms and QoL were assessed. In the second phase (Phase 2), we formed groups of subjects for whom body

plethysmography measurements were available and modeled PD with the Stochastic Lung Model. Numerical modeling was carried out in groups of stable (PD-COPD-S, n=13) and exacerbated (PD-COPD-AE, n=12) COPD patients and healthy volunteers (PD-Controls, n=17). Body plethysmography values were not available in cases where subject's compliance was insufficient.

As a part of the investigation, subjects were asked to fill out questionnaires which included the Modified Medical Research Council (mMRC) dyspnea scale and the Hungarian version of COPD Assessment Test (CAT®). Additionally, participants used the visual analogue scale (VAS).

All individuals were informed about the aims and methods of the study and signed the informed consent form. The study was approved by the ethics committee (TUKEB 239/2015).

3.2. Study design

Subjects performed LF and body plethysmography in a single visit. After a 30-minute-long break, through-device inhalation maneuvers were evaluated using at least three inhaler devices, followed by a second sequence of inhalation maneuvers through each inhaler device. Between the two different sequences, a 5-minute-long break took place. During the breaks we assessed symptoms and quality of life forms were filled. Repeatability of inhalation parameters were calculated between the two subsequent inhalations of each device. PD was modeled later by the Stochastic Lung Model, independently from subject attendance.

3.3. Inhaler devices

Four commercially available inhaler devices were used during through-device measurements in Phase 1: one pMDI (Chiesi®-pMDI), two DPIs (Ellipta® and Genuair®) and on SMI (Respimat®). No active acting agents were applied. In Phase 2 we used three commercially available

inhaler devices (Foster®-pMDI, Trimbow®-pMDI and Spiriva® Respimat®) to determine pulmonary and extrathoracic deposition by numerical modeling.

3.4. Statistical analysis

Statistical analysis was performed using GraphPad Prism Software 8 (GraphPad Software, La Jolla, CA, USA) and SPSS Statistics V22 (International Business Machines Corporation, NY, USA). The results are expressed as the mean ± standard error of the mean (SEM) or median (interquartile range). One-way ANOVA followed by Bonferroni's multiple comparison test or Kruskal-Wallis test with Dunn's multiple comparison test were used as appropriate. Repeatability of deposition values was assessed by the Bland-Altman test. Results were considered to be statistically significant when the p value was less than 0.05.

4. Results

4.1. Clinical characteristics of participants

There were significant differences between COPD patients and the control group in Phase 1 and Phase 2 in terms of age, current smoking habits and cumulative smoking history. Patients with AE were considerably younger and had a higher proportion of current smokers, but had smoked fewer pack years compared to patients in the stable COPD groups. Patients with exacerbation presented more symptoms based on mMRC, CAT® and VAS scores.

4.2. Lung function values

COPD groups exhibited similarly severe airflow obstruction and lung hyperinflation based on LF

parameters, whereas the Control groups in both Phase 1 and Phase 2 had normal LF parameters.

4.3. Through-device parameters and repeatability in Phase 1.

Among the controls, IVCd was lower for all devices, whereas both COPD groups showed only a slight decrease. Notably, both LF-Controls and LF-COPD-AE had significantly lower PIFd compared to PIF during spirometry for all devices. In the LF-COPD-S group, PIFd was significantly reduced only during inhalation through Genuair®. There were no significant differences in IVCd and PIFd between COPD groups for each device.

We observed that in the control groups, PIFd was significantly higher during the second measurement when using Chiesi®-pMDI and Respimat® devices, and there was a trend towards higher values for the second maneuver with Genuair®. Additionally, we noticed a trend towards higher first IVCd with Genuair® in the control group. Interestingly, in the patient group, there was only a

tendency for higher PIFd during the second measurement with Genuair®, but no significant bias in PIFd or IVCd was observed for any inhaler in COPD patients.

4.4. PD, ETD values and repeatability in Phase 2.

Spiriva® Respimat® resulted in significantly higher PD compared to Foster® pMDI and Trimbow® pMDI. For Foster® pMDI and Trimbow® pMDI, similar PD values were observed in PD-Controls, while ETD between PD-Controls and PD-COPD-AE patients showed a significant difference. Spiriva® Respimat® demonstrated significantly lower ETD values than Foster® pMDI and Trimbow® pMDI.

PD was significantly lower in the values calculated from the second measurements in PD-Controls using Foster® pMDI and Trimbow® pMDI. There was a tendency for the second value to be lower in healthy volunteers using Spiriva® Respimat®. No significant difference between the two values was observed in either PD-COPD group for

the two pMDI devices, but in PD-COPD-S patients, the second value tended to be lower, while in PD-COPD-AE patients, it tended to be higher. Coefficient of repeatability (CR) for PD in PD-COPD-S and PD-COPD-AE patients was highest when using Trimbow® pMDI indicating the lowest repeatability.

4.5. Ranking off different inhalers

Furthermore, we conducted a ranking of the four inhalers based in the differences observed between the two measurements of PIF_d and IVC_d in Phase 1 and between the two PD values in Phase 2. In Phase 1, in COPD patients, Respimat® and Genuair® demonstrated the least inter-measurement differences for IVC_d, while Ellipta® and Genuair® exhibited the lowest variability for PIF_d measurements. In Phase 2, consistent with the findings based on the CR values in patients with COPD, Respimat® demonstrated the smallest differences between the two deposition results for PD.

5. Conclusions

1. Comparing LF parameters through four commercially available inhaler devices showed that in healthy controls and exacerbated COPD patients produced significantly lower PIFd values comparing with standard spirometry values. Genuair® showed significantly lower PIFd in stable COPD.

2. The repeatability of inhalation parameters revealed that no significant difference was observed in COPD patients, only in healthy subjects having a lack of experience in inhaler use. However, patients showed individual alterations regarding the difference of the two inhalations through the tested devices.

3. Significantly higher PD and lower ETD values were produced by Spiriva® Respimat ® showed values comparing with Foster® -PMDI and Trimbow® -pMDI. Our results emphasize that in

case of severe COPD patients clinicians can switch from FDTCs to open triple low-resistance inhaler therapy in order to achieve higher deposition of inhaled agents.

4. The repeatability of PD and ETD revealed that FDTC showed the highest CR indicating the lowest repeatability. Individual differences were observed in pulmonary deposition in the three commercially available inhalers.

6. Bibliography of the candidate' publications

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