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Comparison of the clinical effects of combined salmeterol/fluticasone delivered by dry powder or pressurized metered dose inhaler

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ABSTRACT

The salmeterol/fluticasone combination (SFC) inhaler is currently the most widely used maintenance drug for asthmatics worldwide. Although the effectiveness of SFC as either a dry powder inhaler (DPI) or a pressurized metered dose inhaler (pMDI) is well documented, there is limited data comparing the clinical efficacies of the two devices. To address this issue, we carried out a randomized crossover trial in which asthmatic patients (n = 47; mean age, 62.5 ± 16.5 years old) received a 12-week treatment of SFC DPI (50/250 μg twice daily) or SFC pMDI (four puffs of 25/125 μg daily). After a 4-week washout period, patients received another crossover treatment for 12 weeks. Respiratory resistance and reactance were measured by forced oscillation technique (MostGraph-01), spirometry, fractional exhaled nitric oxide (FeNO), and an asthma control test (ACT) every 4 weeks. The mean forced expiratory volume$_{1.0}$ at the baseline was 2.16 ± 0.86 (L). Respiratory system resistance at 5 Hz (R5), the difference between R5 and R at 20 Hz (R5 − R20), and FeNO improved in both treatment groups, while reactance at 5 Hz (X5) and ACT score improved only in the pMDI group. In patients >70 years old (n = 21), R5, R5 − R20, ΔX5, and FeNO improved only in the pMDI group. These results suggest that SFC by pMDI produces a stronger anti-inflammatory and bronchodilatory effect even in patients whose asthma is well controlled by SFC delivered by DPI.

1. Introduction

Asthma is a global public health problem that affects up to 300 million people worldwide [1]. Despite recent advances in pharmacological therapies, under-treatment of asthma remains common, especially in terms of long-term maintenance regimens targeting airway inflammation. Although inhalation is an effective delivery route for bronchodilators as well as inhaled corticosteroids (ICS), many asthmatics—especially elderly patients—still have difficulty in using the inhaler correctly. This along with poor adherence to treatment programs are thought to be common causes of uncontrolled asthma [2,3]. Available types of inhaler device for ICS and long-acting β_2 agonist (LABA) combination therapy now include the dry powder inhaler (DPI) and pressurized metered-dose inhaler (pMDI). Although device preparation and handling techniques vary among brands, some generalizations can be made with regard to optimal inhalation procedure for each type of device: inhalation should be slow and steady with the pMDI, but sharp and rapid with the DPI [4,5]. Additionally, the particle size of each preparation—i.e., mass median aerodynamic diameter—may impact treatment outcome [6]. It has been reported that particle sizes are smaller for pMDI than for DPI products, such that the former can be more widely distributed from central to peripheral airways [7]. However, there have been few clinical trials comparing inhalers for license–equivalent combinations of ICS/LABA.

The salmeterol/fluticasone combination (SFC) inhaler is currently the most widely used product by persistent asthmatics for maintenance therapy. Although the effectiveness of both SFC

Abbreviations: ACT, asthma control test; BUD/FM, budenoside/formoterol; DPI, dry powder inhaler; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; FEV, forced expiratory volume; FOT, forced oscillation technique; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; pMDI, pressurized metered dose inhaler; R5 (20), respiratory system resistance at 5 (20) Hz; R5−R20, difference between R5 and R20; SFC, salmeterol/fluticasone combination; X5, reactance at 5 Hz.

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DPI and pMDI is well documented, there is limited data comparing their clinical effects, with most studies reporting similar outcomes for the two devices [8–11], and it has been reported that the particle size of SFC pMDI is about half that of DPI [6].

Small airways are difficult to investigate owing to their inaccessibility; several tests are currently available to assess small-airway dysfunction [7]. Reviews of the benefits and limitations of each test have concluded that there is no gold standard for evaluation [12,13]. The forced oscillation technique (FOT) is a noninvasive method that measures respiratory impedance—i.e., the spectral relationship between pressure and airflow. The impulse oscillation system (IOS) is a commercially available version of the FOT that offers respiratory impedance at a wide range of frequencies. MostGraph is a new method of FOT that employs 3-dimensional color images along a time axis to visualize respiratory cycle dependence [14]. MostGraph was recently recognized as a useful tool for evaluating small-airway dysfunction in chronic obstructive pulmonary disease (COPD) and asthmatic patients [15–20], and was therefore used in the present study.

The aim of the present study was to compare the anti-inflammatory or bronchodilatory effect of SFC administered by DPI and pMDI on peripheral small airways in the clinical setting. We hypothesized that the pMDI product with its smaller particle size which might reach peripheral small airways could improve asthma control in patients in which this has already been achieved using a DPI product even in patients with fixed airflow limitation or who are elderly.

2. Methods

2.1. Subjects

The study subjects included outpatients at the National Center for Global Health and Medicine aged ≥20 years old with persistent, moderate asthma treated for at least 6 months with a ICS/LABA combination inhaler (equivalent fluticasone propionate ≤ 500 μg/day) and in whom the disease was well or totally controlled—i.e., an Asthma Control Test (ACT) score of 20–25 points. Asthma was diagnosed according to clinical history and based on pulmonary function tests demonstrating variable airflow obstruction by measuring bronchodilator responsiveness, or bronchial hyperreactivity by assessing the response to methacholine challenge, which satisfied the criteria of the Global Initiative for Asthma [1]. Patients with non-reversible lung diseases such as COPD or interstitial pneumonitis were excluded from the analysis.

2.2. Study design

The study was a prospective randomized crossover trial. Written, informed consent was obtained from each patient. At first, the patients were divided into two groups based on co-existence of seasonal allergic rhinitis or not to exclude seasonal variation of the fractional exhaled nitric oxide (FeNO) value, which was higher during the pollen scattering than during the non-pollen-scattering season. In this subgroup, after a 4-week washout period with budesonide/formoterol (BUD/FM) combination DPI (320/9 μg/day, Turbuhaler), patients were randomized to receive a 12-week treatment of a SFC DPI (250 μg, two puffs/day, Diskus) or SFC pMDI (125 μg, four puffs/day). After another 4-week washout period, patients received a second crossover treatment for 12 weeks (Fig. 1). The randomization was made based upon computer-generated table of random numbers. At each visit, inhalation technique and adherence to the regimen were verified. The patients with adherence rate less than 80% in wash-out period were excluded. Patients receiving the SFC pMDI were advised to use antistatic Aero-Chamber Plus as an assistant spacer to produce high availability [21].

The primary end point was the change of respiratory system resistance (R) and reactance (X) before and after 12 weeks of treatment, as measured using MostGraph-01 (Chest MI, Tokyo, Japan). More than 5 technically acceptable MostGraph measurement were performed. Pulmonary function tests are measured by using spirometer (model CHESTAC-8100; CHEST MI, Inc., Tokyo, Japan) at the same visit. FeNO was measured 0, 4, and 12 weeks after treatment using NIOX-MINO (Aerocrine, Solna, Sweden) before any forced expiratory maneuvers; the best value of three readings was used for analysis. All medications for maintenance therapy and short-acting β2 agonists for reliever use were halted 12 h before Spirometry, MostGraph and FeNO measurements, which were performed in the same order at similar times of the day before inhalation of the morning dose. ACT score and patient preference for the product (DPI, pMDI, or BUD/FM) were also recorded.

R at 5 and 20 Hz (R5 and R20, respectively) was measured and the difference between them (R5–R20) was taken as an indicator of the frequency dependence of R, which is presumed to reflect non-homogeneous ventilatory mechanics. We also determined X at 5 Hz (X5), which reflects elastic and inertial properties of the lung; resonant frequency (Fres), which is the point at which X = 0 and elastic and inertial forces are equal in magnitude and opposite; and low-frequency reactance area, which is the integral of X5 to Fres. Each oscillatory index was expressed as the mean values during a respiratory cycle (whole breath) and the differences between inspiratory and expiratory phases. To clarify the difference of clinical effects among elderly patients between DPI and pMDI, the subdivision in patients aged ≥70 and < 70 years old were made and analyzed.

2.3. Statistical analysis

It was determined that a total sample size of 16 subjects per group would provide 80% power at a 2-sided α level of 0.05 to detect a difference of 1 $cmH_2O/L/s$ or greater in R5 (a primary end point), assuming an SD of 1 $cmH_2O/L/s$. And we expected some variables concerning respiratory resistance which might be related to peripheral airway could be change after treatment. Values are presented as mean ± SD. Differences between groups were evaluated for significance using the χ^2 and Mann–Whitney U tests. Comparisons between baseline and measured values were assessed by repeated-measures analysis of variance. All analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC, USA).

The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki (revised in 2008). The study protocol was approved by the Ethics Committee of the National Center for Global Health and Medicine (NCGM-G-001321-00). The clinical trial registration number was UMIN000009990.

3. Results

Three of the 50 patients enrolled in the study dropped out due to an adverse event; 2 cases hoarseness, and 1 case cough after inhalation. We therefore analyzed data from 47 patients. The male-to-female ratio was 28:19; the mean age was 62.5 ± 16.5 years (range: 24–78 years); mean disease duration was 16.8 ± 14.5 years; and % predicted value of forced expiratory volume $(FEV)_{1.0}$ was 68.0% ± 14.1%. Concomitant medications were leukotriene receptor antagonist in 19 patients and a theophylline preparation in six patients. The mean ACT score of 23.6 indicated that asthma was