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Effect of inhaled corticosteroids on small airways in asthma: Investigation using impulse oscillometry

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ABSTRACT

Background: Small airways appear to have an important role in asthma. Hydrofluoroalkane-134a beclomethasone dipropionate (HFA-BDP) has ultrafine particles and accordingly greater deposition in the small airways than chlorofluorocarbon (CFC)-BDP. Impulse oscillometry systems (IOS), a new and non-invasive measure of pulmonary function, can examine the resistance of total (R5), large (R20), and small airways (R5–R20) separately, and low-frequency reactance area (AX), also considered a measure of small airways dysfunction.

Methods: Mild-to-moderate asthmatics who were inhaled corticosteroid naïve were randomized to receive 200 mcg HFA-BDP bid ($n = 26$) or 400 mcg CFC-BDP bid ($n = 12$) for 12 weeks in an open-label manner. Following baseline measurements, IOS and spirometry were repeated every 4 weeks, and methacholine challenge to separately assess airway sensitivity and airway reactivity and lung volumes at 12 weeks.

Results: Moderate correlations were found between R5–R20 or AX and spirometry and lung volume indices of small airways, and between R20 and peak expiratory flow at baseline. The two groups did not significantly differ in baseline clinical or functional parameters. At 12 weeks, all IOS indices improved in the HFA-BDP group, whereas all but R5–R20 improved with CFC-BDP. R5–R20 and AX progressively improved with HFA-BDP; these changes achieved statistical significance at 12 weeks versus the CFC-BDP group. Other IOS and spirometry indices failed to show such trends. HFA-BDP significantly attenuated methacholine airway sensitivity; the degree of this attenuation strongly correlated with R5–R20 and AX baseline values, and with improvement of AX with treatment.

Conclusion: HFA-BDP is an effective treatment of small airways in asthma. Prolonged treatment provides a progressive effect over time, which is associated with an attenuation of airway responsiveness.

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1. Introduction

Asthma is characterized by chronic airway inflammation and associated airway hyperresponsiveness. Inflammation extends from large to small airways [1–5], being more intense in the latter [2,3]. Patients with nocturnal asthma exhibit a significant influx of eosinophils to the small but not the large airways in the early morning, in association with a fall in FEV_1 [2,6]. Air trapping, a high-resolution computed tomography (HRCT) index of small airway disease, significantly correlates with the severity of asthma and airway hypersensitivity [7]. Small airways may thus be an important therapeutic target [8].

Inhaled corticosteroids (ICSs) are highly effective anti-inflammatory medications in asthma. However, some patients continue to have persistent symptoms despite high-dose ICS treatment. This may be attributed, at least in part, to poor delivery of ICS to the small airways leading to insufficient control of inflammation. Reformulation of beclomethasone dipropionate (BDP) with hydrofluoroalkane-134a (HFA) allows delivery of aerosol with much finer particles (mass median aerodynamic diameter (MMAD) of 1.1 μm) than those of conventional chlorofluorocarbon-11/12 (CFC)-BDP (3.5 μm), and this results in particles being deposited further into the lung periphery [9].

The effect of HFA-formulations of ICS on small airways in asthma has been investigated in several small studies [10–14]. The addition

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of 320 μg HFA-BDP daily for 12 weeks had greater benefits on closing volume, closing capacity, and mid-forced expiratory flow ($FEF_{25-75\%}$) than the addition of 330 μg CFC-fluticasone (MMAD 2.4 μm) daily [10]. Moreover, 4 weeks' treatment with 200 μg HFA-BDP daily resulted in greater improvement of air trapping on HRCT assessed after methacholine inhalation than 200 μg CFC-BDP daily [11]. Furthermore, 680 μg HFA-flunisolide (MMAD 1.2 μm) daily for 6 weeks attenuated eosinophilic inflammation of large and small airways as assessed by endobronchial and transbronchial biopsies [12]. However, the differential and progressive effects of ICS on large and small airways remain poorly known, in part because of methodological limitations of previous studies. The invasiveness of biopsy and the radiation exposure associated with CT preclude repeated measurements over time. Dose–response studies of ICS have indicated that small airways may require longer-term treatment to obtain maximal effect [13], but evidence is lacking [14].

The impulse oscillometry system (IOS) is a non-invasive, effort-independent and thus repeatable measure to assess airway function [15]. IOS has a potential to examine respiratory resistance (R) and respiratory reactance (X) of large and small airways separately [15], and it is more sensitive to therapeutic intervention than spirometry [16]. Here we compared HFA-BDP and CFC-BDP in terms of the progressive effect of 12 weeks' treatment on pulmonary function in asthmatic patients as assessed by IOS. Spirometry, lung volumes, and the two components of airway responsiveness, airway sensitivity and reactivity, were also examined.

2. Materials and methods

2.1. Subjects

We consecutively enrolled 48 ICS-naïve adults with mild-to-moderate asthma, who were referred to our asthma clinic of Kyoto University. Asthma was diagnosed according to the American Thoracic Society criteria [17]. The patients were lifetime nonsmokers or had smoked <5 pack-years and had quit for >12 months. None had a history or abnormal chest X-ray findings suggestive of concomitant respiratory disease.

This study was approved by the Ethics Committee at our institution, and written informed consent was obtained from all patients.

2.2. Study design

This was a 12-week, randomized, open-label study to compare the effects of HFA-BDP (QVAR, Schering-Plough, Tokyo, Japan) and CFC-BDP (ALDECIN, Schering-Plough, Tokyo, Japan). Baseline characteristics were assessed during a one-week run-in period during which patients were allowed to use only short-acting β_2-agonists. Patients were then randomly assigned to receive either HFA-BDP (400 μg daily) or CFC-BDP (800 μg daily) [18] at a ratio of 2:1 [19]. This was due to an ethical reason based on the predominance in the efficacy of HFA-BDP over that of CFC-BDP already shown by several studies [20,21]. Other than ICS, on-demand use of β_2-agonists was permitted but was withheld for 6 h before measurements. IOS and spirometry measurements were repeated at 4, 8, and 12 weeks, while lung volume measurement, methacholine challenge and symptom questionnaires [11] were repeated at 12 weeks (Fig. 1). Pre-bronchodilator lung function values were used for analysis.

2.3. Conventional pulmonary function tests

Forced expiratory volume in one second (FEV_1), mid-forced expiratory flow ($FEF_{25-75\%}$), peak expiratory flow (PEF), residual volume (RV), and RV/total lung capacity (TLC) were measured.

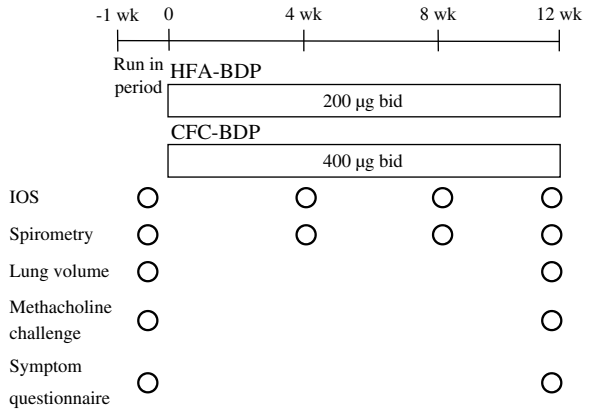

Fig. 1. Study design. HFA-BDP = hydrofluoroalkane-134a beclomethasone dipropionate; CFC-BDP = chlorofluorocarbon-11/12-BDP; IOS = impulse oscillometry system.

2.4. Methacholine challenge

Airway responsiveness was examined by continuous inhalation of methacholine and simultaneous measurement of R (Astograph™, Chest, Tokyo, Japan) [22,23]. The parameters of airway sensitivity (Dmin) and airway reactivity (SRrs) were measured separately [7,23].

2.5. Impulse oscillometry system

Respiratory impedance was measured using a Jaeger MasterScreen IOS™ (Erich Jaeger, Hoechberg, Germany), according to standard recommendations [24]. Rectangular mechanical impulses containing the whole frequency spectrum were applied to the respiratory system through a mouthpiece during quiet breathing. The resulting pressure and volume signals were analyzed for amplitude and phase differences to determine R and X of the total respiratory system. Impedance measurements included R and X from 5 to 35 Hz (R5–R35 and X5–X35) and frequency of resonance, which represents the point at which the usually negative reactance reaches 0. Pressure oscillations at frequencies >15 Hz are severely damped out before reaching peripheral airways, while those at frequencies <10–15 Hz penetrate much further into the lung periphery [15]. We used R5, R20, and R5–R20 as indices of total, large, and small airway resistance, respectively [15,25–27]. In addition, integrated area of low-frequency X (AX) was examined as a sensitive measure of small airways obstruction [15,25–27].

The primary outcome of the study was defined as the variation of IOS indices associated with treatment. The secondary outcome included the variation of spirometry indices, lung volume indices, airway responsiveness and symptoms before and after treatment, and correlations of treatment-related changes among variables. Moreover, to confirm the validity of R20, and R5–R20 and AX as measures of large and small airways, respectively, correlations between these IOS indices and conventional measures of large (PEF) and small airways ($FEF_{25-75\%}$, RV, and RV/TLC) were analyzed.

2.6. Statistical analysis

Values are presented as means (SD) or medians (range). Comparisons between groups were made with the Mann–Whitney *U*-test. All paired within-subject data were analyzed using the Wilcoxon signed-rank test. Effect of treatment at each time point was compared between groups with an unpaired *t*-test by

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