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Persistent elevation of exhaled nitric oxide and modification of corticosteroid therapy in asthma

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ABSTRACT

Background: Persistent airway inflammation, detected by fractional exhaled nitric oxide (FE_{NO}), is occasionally observed in asthmatic patients, even in those treated with inhaled corticosteroids (ICS). However, improvement in residual airway inflammation and pulmonary function through modification of corticosteroid therapy has not been proven.

Methods: Thirteen asthmatic patients whose FE_{NO} levels were over 40 parts per billion (ppb), despite dry-powder ICS therapy, were enrolled. A 3-step change in steroid treatment was undertaken until FE_{NO} was less than 40 ppb. In the first step, the powder formula was changed to an ultra-fine particle compound as an equipotent ICS dose. In the second step, the ICS dose was doubled. In the third step, oral corticosteroids were added. We measured pulmonary function and FE_{NO} and alveolar NO concentrations (CAlvNO).

Results: Doubling the ICS dose and changing the ICS formula significantly improved FVC ($p<0.001$), FEV1 ($p<0.05$), the slope of the single nitrogen washout curve (dN_2) ($p<0.01$), FE_{NO} ($p<0.001$), and CAlvNO ($p<0.05$), relative to baseline. The reductions in FE_{NO} were significantly associated with the improvement in airflow limitation assessed by dN_2 ($r=0.73$, $p=0.007$). The remaining FE_{NO} elevation, even after doubling the ICS dose, did not decrease after oral corticosteroid administration.

Conclusions: These results suggest that modification of ICS therapy can suppress residual FE_{NO} elevation, and that reduction in FE_{NO} levels is associated with improvement in airflow limitation. However, steroid-resistance mechanisms may exist in some asthmatic patients with sustained FE_{NO} elevations.

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Abbreviations: CAlvNO, alveolar NO concentration; DPI, dry-powder inhaler; dN_2, slope of single nitrogen washout curve; eNO, exhaled nitric oxide; FE_{NO}, fractional exhaled nitric oxide; FP, fluticasone propionate; ICS, inhaled corticosteroid; ppb, parts per billion; SFC, salmeterol/fluticasone combination; n.s., not significant; r, correlation coefficient.

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1. Introduction

Airway inflammation is a very important part of the pathophysiology of asthma [1,2]. Fractional exhaled nitric oxide is increasingly being used as a surrogate marker for airway inflammation because the values provide information about the cause of asthma in these patients [3]. Several previous studies have shown that increased levels of FE_{NO} are related to a loss of asthma control and an accelerated decline in pulmonary function [4–7]. More recently, it has been suggested that persistently high FE_{NO} level in steroid-treated asthmatic individuals may also reflect a highly reactive phenotype, and such patients should be managed with caution [8,9]. However, the effectiveness of sequential measurement of FE_{NO} to guide adjustment of anti-inflammatory therapy for asthma is controversial [10,11].

Corticosteroids effectively suppress eosinophilic inflammation, and inhaled corticosteroids (ICS) are widely used for long-term management of asthma [12]. Furthermore, ICS/long-acting β_2-agonist (LABA) combinations have also been developed, their efficacy is more pronounced than that of previous therapies [13]. However, some asthma patients show persistent airway inflammation and pulmonary dysfunction despite ICS treatment [14,15]. Thus far, the ability of the modification of corticosteroid therapy to improve airway inflammation and pulmonary function in asthmatic patients with sustained FE_{NO} elevations has not been fully elucidated.

In this prospective interventional study, modification of steroid therapy included three steps: changing the powder formula to an ultra-fine particle compound, doubling the dose, and administering oral prednisolone. We assessed airway inflammation by using measurement of exhaled NO (eNO) and pulmonary function by using spirometry and single nitrogen-washout curve to determine the relationship between the changes in eNO and pulmonary function facilitated by modification of steroid therapy.

2. Methods

2.1. Study subjects

Thirteen stable patients with asthma were recruited from the outpatient clinic at Wakayama Medical University Hospital. All subjects were diagnosed with asthma by a pulmonologist and had documented reversible airflow limitation. All subjects had adequate inhalation and good adherence to asthma therapy. Patients were included in the study if their eNO levels at a flow rate of 50 mL/s (FE_{NO}) were persistently over 40 parts per billion (ppb) despite receiving conventional asthma therapy, including dry powder-inhaled (DPI) corticosteroids. Subjects were excluded if they had an exacerbation of asthma 3 months prior to the study; if they had other pulmonary disease, including chronic obstructive pulmonary disease, allergic bronchopulmonary aspergillosis, and allergic and granulomatous angitis; or if they had esophageal reflux, vocal cord dysfunction, or bronchiectasis that could influence asthma control. All patients received an explanation of the study protocol and gave written informed consent. This study was performed in conformance with the Declaration of Helsinki and was approved by the local ethics committee at Wakayama Medical University (IRB #526: February 15, 2008). The study was registered at the University Hospital Medical Information Network (UMIN 000008401).

2.2. Study design

This was a prospective interventional study for assessing the effect of the augmentation of steroid therapy on airway inflammation and pulmonary function in asthmatic patients with persistently high FE_{NO} (Fig. 1). The augmentation of steroid treatment included three steps: (1) changing the powder formula to an ultra-fine particle compound, (2) increasing the dose two-fold, and (3) administering oral corticosteroids in addition to changing the ICS formula. In step 1, ciclesonide, which is formulated as a solution to be delivered via a hydrofluoroalkane-134a metered-dose inhaler, was given at a dose equivalent to the regularly used DPI corticosteroid dose at the beginning of the study. In step 2, the ciclesonide dose was increased two-fold if FE_{NO} was still over 40 ppb after step 1. In step 3, if FE_{NO} was still over 40 ppb after step 2, oral prednisolone (0.5 mg/kg) was administered for 2 weeks. Based on our recent study [9], we selected 40 ppb as the cutoff point for high and low FE_{NO} in this analysis, a value that was within previously published cutoff points [8,16–18].

2.3. Exhaled NO measurement

The level of eNO was measured in accordance with the recommendations of the current guidelines [19]. We measured eNO in triplicates prior to spirometry at four separate, constant expiratory flow rates (50, 100, 175 and 370 mL/s) by using a chemiluminescence-based exhaled NO analyzer (NA-623 N, Chest Co. and Kimoto Electric Co., Tokyo, Japan), and the mean of three values was reported. Measurements were included if an adequate NO plateau could be measured or if the NO levels were above the detection limit. The NO analyzer was calibrated monthly with a known concentration (748 ppm) and before examining each patient with NO-free air. The technique of Tsoukias and George was used to calculate the peripheral airway/alveolar NO concentration (CAlvNO, ppb) (slope) by using a linear regression line for each subject with a minimum of three expiratory flow rate data points [20]. To adjust for possible spurious overestimation of values for peripheral lung CAlvNO, the initial, uncorrected large airway NO flux (nL/s) was divided by a correction factor and subtracted from the initial uncorrected small airway/alveolar CAlvNO [21]. Because FE_{NO} is perhaps one of the fastest responding markers and the decrease in FE_{NO} levels after corticosteroid use is rapid [22], we selected 4-and 2-week intervals for the examination.

2.4. Pulmonary function testing

Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were measured as previously described [23]. Single-breath nitrogen (SBN_2) test was performed (CHESTAC-7800, Chest Co., Tokyo, Japan) according to previously described methods [24]. In order to minimize inter-observer variability,

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