Dear Editor,

Airway hyperresponsiveness in bronchial asthma is commonly evaluated by inhalation of methacholine (Mch) or histamine. Asthma patients also show bronchoconstriction upon adenosine inhalation. Inhaled adenosine 5′-monophosphate (AMP) is converted immediately to adenosine by 5′-nucleotidase in the mucosa of the respiratory tract, which activates mast cells (MCs). Direct bronchial provocation with AMP causes immediate increases in the concentrations of prostaglandin D₂, histamine, and tryptase in the bronchoalveolar lavage fluid of asthma patients compared with healthy volunteers. Premedication with the MC-stabilizing drugs cromolyn and nedocromil has been shown to reduce AMP-induced bronchoconstriction by 9.6- and 22.2-fold, respectively.

Based on the reports mentioned above, we postulated that AMP-induced bronchoconstriction is an indirect effect of the histamine and prostaglandins generated by MC degranulation. This type of bronchoconstriction by AMP may occur via a different mechanism compared with bronchoconstriction induced by Mch (which stimulates airway smooth muscle directly).

Aspirin-intolerant asthma (AIA) is a type of refractory bronchial asthma. Even under stable conditions, the number of MCs in the airway mucosa of AIA patients is 2.5-fold greater than that in non-AIA patients. Furthermore, levels of a marker of MC activation, urinary 9α,11β-prostaglandin F₂α, are significantly higher in AIA patients. Based on these findings, we hypothesized that MCs would show greater activation in AIA than in non-AIA, and that AIA patients would be more hypersensitive to AMP compared with non-AIA patients. To test these hypotheses, we compared the results of inhalation challenge tests using AMP and Mch conducted in patients with bronchial asthma diagnosed with AIA or non-AIA.

The Ethics Committee of Fujita Health University (Toyoake, Aichi, Japan) approved our study protocol. Study participants were 30 patients treated for bronchial asthma at an outpatient clinic in our hospital. Patients who reported an infection of the upper respiratory tract or attack of bronchial asthma within 4 weeks before the examination were excluded from the study. Among these 30 patients, 12 were diagnosed with AIA (4 males and 8 females; mean age, 42.6 years) and 18 with non-AIA (5; 13; 42.1 years). Characteristics, laboratory findings, and therapy of studied patients are shown in Table 1.

The diagnosis of AIA was confirmed by: inhalation provocation tests using tolmetin or sulpyrine; oral aspirin provocation test with a history of asthma attacks induced by nonsteroidal anti-inflammatory drugs (NSAIDs). Patients with a negative result of the inhalation challenge test using sulpyrine/tolmetin, or oral aspirin provocation test with no history of NSAID intolerance, were classified as “non-AIA”.

For the bronchial provocation test, AMP chloride and Mch (Sigma–Aldrich; Saint Louis, MO, USA) were dissolved in physiologic (0.9%) saline in gradually increasing concentrations. Each dilution was inhaled using a nebulizer, and was interrupted if the forced expiratory volume in 1 s (FEV₁) decreased by 20% from its baseline value. A concentration of Mch and AMP that achieved a fall in FEV₁ of 20% (PC₂₀) was defined as the index for airway hyperresponsiveness.

Statistical analyses were undertaken using JMP v8.0 (SAS Institute, Cary, NC, USA). The Mann–Whitney U-test was used to determine differences in lung function, sex, age, immunoglobulin (Ig)E value, Mch and AMP thresholds (PC₂₀-Mch and PC₂₀-AMP, respectively) for airway hyperresponsiveness, and the ratio of PC₂₀-AMP/PC₂₀-Mch between AIA and non-AIA. We used ANCOVA to compare the regression coefficient between logPC₂₀-AMP and logPC₂₀-Mch in AIA and non-AIA. p < 0.05 was considered significant.

Table 1

| Age (mean ± SD) | 42.6 ± 17.0 | 42.1 ± 14.9 | n.s. |
| Male | 4 | 5 | n.s. |
| Atepy (=–) | 6/3 | 12/6 | n.s. |
| Severity (mild/moderate) | 5/7 | 7/10 | n.s. |
| PVC (ml, mean ± SD) | 3006 ± 586 | 3085 ± 722 | n.s. |
| FEV₁.0 (ml, mean ± SD) | 2430 ± 537 | 2365 ± 602 | n.s. |
| FEV₁.0% (%, mean ± SD) | 81.4 ± 9.2 | 77.2 ± 6.8 | n.s. |
| %FEV₁.0 (%, mean ± SD) | 90.3 ± 14.3 | 85.5 ± 13.3 | n.s. |
| WBC (μl, mean ± SD) | 6300 ± 1500 | 6900 ± 2200 | n.s. |
| Eosinophil (%, mean ± SD) | 9.2 ± 6.3 | 6.5 ± 2.9 | n.s. |
| IgE (U/ml, mean ± SD) | 285.5 ± 272.4 | 421.3 ± 404.9 | n.s. |
| Therapy | n.s. |
| ICS (μg, mean ± SD) | 420 ± 261 | 360 ± 214 | n.s. |
| LABA (n) | 6 | 5 | n.s. |
| Theophylline (n) | 9 | 13 | n.s. |
| LTRA (n) | 10 | 14 | n.s. |

n.s., not significant; ICS, inhaled corticosteroid; LABA, long acting beta agonist; LTRA, leukotriene receptor antagonist; SD, standard deviation; WBC, white blood cells; FEV₁, forced expiratory volume; AIA, aspirin-intolerant asthma.

Letter to the Editor

Increased airway hyperresponsiveness to adenosine in patients with aspirin intolerant asthma

Peer review under responsibility of Japanese Society of Allergology.
Between AIA and non-AIA, there were no significant differences with regard to clinical background and lung function (Table 1). There were no significant differences in PC20-AMP and PC20-Mch between the two groups (data not shown). However, the ratio of PC20-AMP/PC20-Mch was significantly lower than that observed in non-AIA patients (Mann-Whitney U-test, p = 0.007) (Fig. 1A). A significant positive correlation was observed between logPC20-AMP and logPC20-Mch in AIA and non-AIA patients (r = 0.781 and 1.117, respectively, p < 0.001) (Fig. 1B). Comparative analyses of the two regression slopes showed that individual PC20-AMP/PC20-Mch was significantly lower in AIA than in non-AIA (p = 0.02) (Fig. 1B). These results suggested that sensitivity to AMP was significantly higher in AIA patients compared with non-AIA patients (Mann-Whitney U-test, p = 0.007) (Fig. 1A).

AIA patients exhibit more severe asthmatic symptoms than non-AIA patients, so the diagnosis and appropriate treatment of AIA patients is important. A NSAID-challenge test is essential for the diagnosis of AIA, but is associated with problems such as sensitivity, specificity, and risks. Thus, several trials to investigate better diagnostic methods for AIA have been reported. These trials included in vitro diagnostic methods such as arachidonic-acid derivatives in peripheral blood polymorphonuclear leukocytes or cluster of differentiation (CD)11b expression on the eosinophil surface.

Our study suggests that AIA patients may be more sensitive to AMP-induced bronchoconstriction than non-AIA patients, and that bronchial hypersensitivity measured by Mch inhalation was similar in AIA and non-AIA patients. We speculate that the AMP provocation test may reflect MC activation in the airways of AIA patients. Differential hyperresponsiveness of airways to inhalation of AMP and Mch might be a useful marker to distinguish AIA from non-AIA.

Acknowledgments

The authors thank Mrs. Naomi Maeda for her excellent secretarial help. They also thank Mrs. Chikako Hibiya and Ms. Noriko Hiramatsu for their generous technical assistance.

Conflict of interest

The authors have no conflict of interest to declare.

Letter to the Editor / Allergology International xxx (2016) 1–3
Sumito Isogai a, Yoshikazu Niwaa, Hiroshi Yatsuya b, Masamichi Hayashi a, Naoki Yamamoto a, Takuya Okamuraa, Tomoyuki Minezawaa, Yasuhiro Gotoa, Teppei Yamaguchia, Tomoko Takeyama a, Yosuke Sakakibara a, Sayako Morikawaa, Tomoya Horiguchia, Yusuke Gotoha, Yuki Mienoa, Sakurako Uozua, Toru Nakanishia, Mitsushi Okazawad, Hiroki Sakakibarae, Kazuyoshi Imaizumia

a Department of Respiratory Medicine, Fujita Health University, Aichi, Japan
b Department of Public Health, Fujita Health University, Aichi, Japan
c Laboratory of Molecular Biology & Histochemistry, Fujita Health University, Aichi, Japan
d Department of Respiratory Medicine, Daiyukai General Hospital, Aichi, Japan
e Tokushige Respiratory Clinic, Aichi, Japan

* Corresponding author. Department of Respiratory Medicine, Fujita Health University, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan.
E-mail address: isogai@fujita-hu.ac.jp (S. Isogai).

References


Received 19 April 2016
Received in revised form 16 September 2016
Accepted 26 September 2016
Available online xxx