

Beneficial Effect of Combination Therapy with Ozagrel and Pranlukast in Exercise-induced Asthma Demonstrated by Krypton-81m Ventilation Scintigraphy—A Case Report

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Abstract

Introduction: We evaluated the effect of combination therapy with thromboxane A₂ synthesis inhibitor and leukotriene receptor antagonist in a patient with exercise-induced asthma using krypton-81m ventilation scintigraphy. **Clinical Picture:** In a patient with exercise-induced asthma, we found exercise-induced abnormalities of respiratory function test and ventilation scintigraphy, and increases in plasma concentrations of thromboxane B₂ and leukotriene C₄ with exercise. **Treatment:** A thromboxane A₂ synthesis inhibitor (ozagrel) and a leukotriene receptor antagonist (pranlukast) were prescribed. **Outcome:** After treatment for 2 weeks, abnormalities of respiratory function test and ventilation scintigraphy improved. **Conclusions:** The combination therapy with ozagrel and pranlukast might be useful for the relief of symptoms in patients with exercise-induced asthma, and krypton-81m ventilation scintigraphy could be a useful tool for visible evaluation of treatment.

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Key words: Leukotriene C₄, Leukotriene receptor antagonist, Thromboxane A₂ inhibitor, Thromboxane B₂

Introduction

Exercise is a common stimulus of bronchoconstriction in subjects with asthma.¹⁻⁴ Exercise-induced asthma is a temporary increase in airway resistance that occurs after several minutes of strenuous exercise, usually after the exercise has ceased. The exact mechanism causing exercise-induced asthma has not yet been fully elucidated, but alterations in the temperature of the airway or in the osmolality of the epithelial-lining fluid during exercise have been proposed as a possible mechanism.^{5,6} It has been reported recently that these changes cause the release of constrictor mediators, such as leukotrienes and thromboxane, resulting in the development of bronchoconstriction.⁷⁻¹⁰

Krypton-81m ventilation scintigraphy has been shown to be useful in the evaluation of short-time changes in ventilation.¹¹⁻¹³ We present a case of exercise-induced asthma in which krypton-81m ventilation scintigraphy proved to be useful in evaluation of treatment with the combination of a thromboxane synthesis inhibitor and a leukotriene receptor antagonist.

Case Report

A 64-year-old woman with a 10-year history of hypertension and hyperuricaemia was admitted to our hospital complaining of dyspnoea and chest discomfort on effort. She was receiving amlodipine for hypertension and allopurinol for hyperuricaemia. She was not a smoker. Physical examination revealed a blood pressure of 132/84 mmHg and a regular heart rate of 62 beats/min. She had never had a diagnosis of bronchial asthma, and auscultation of the heart and lungs revealed no murmurs or rhonchi. The electrocardiogram showed incomplete right bundle branch block, but no obvious ST segment abnormality. The chest roentgenogram and ultrasound cardiac echocardiography did not show any obvious abnormalities. Coronary angiography showed no critical stenosis, and a provocation test with acetylcholine was negative. Arterial blood gas analysis at resting condition was normal and respiratory function test showed slightly reduced % predicted FEV₁ (74%, Table I). We measured oxygen saturation from arterial blood gas sampling during exercise with a bicycle ergometer. Monitoring of oxygen saturation during exercise

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TABLE I: RESPIRATORY FUNCTION TESTS AT REST AND AFTER EXERCISE BEFORE AND AFTER TREATMENT

	Before treatment			After treatment		
	Rest	After exercise	% change	Rest	After exercise	% change
VC (L)	2.06	2.00	-3	2.17	2.06	-5
% predicted VC (%)	88	86		94	89	
FEV ₁ (L)	1.32	0.89	-32.5	1.42	1.23	-13.3
% predicted FEV ₁ (%)	74	50		81	70	

VC: vital capacity, FEV₁: forced expiratory volume in one second

revealed marked hypoxaemia associated with a complaint of dyspnoea (Fig. 1). We speculated that the exercise-induced hypoxaemia might be caused by respiratory disturbance associated with exercise. Hence, we performed inhaled krypton-81m ventilation scintigraphy and perfusion scintigraphy with intravenous injection of 99m-technetium-MAA at rest and 10 minutes after exercise to evaluate respiratory disturbance. Although both ventilation and perfusion images were normal at rest, regional ventilation abnormality was found after exercise, suggesting regional bronchoconstriction induced by exercise (Fig. 2). Thus, the ventilation-perfusion mismatch following exercise might be the likely mechanism that contributed to the fall in oxygen saturation after exercise. Respiratory function tests repeated at rest and after exercise revealed a decrease in FEV₁ from 1.32 L at rest to 0.89 L after exercise. The percentage decrease in FEV₁ (32.5% versus at rest) is greater than 15%, which is the value defined as the criteria for exercise-induced asthma.¹⁴

On a different day, ergometer exercise was repeated to evaluate the role of leukotriene or thromboxane in the exercise-induced bronchoconstriction in this case. Plasma

concentrations of thromboxane B₂, which is a stable metabolite of thromboxane A₂, and leukotriene C₄ were measured at rest, during and after exercise using radioimmunoassay (RIA). Thromboxane B₂ and leukotriene C₄ were measured using [¹²⁵I] RIA kit (NEN Life Science Products Inc, Boston, MA, USA) and leukotriene C₄ specific [³H] RIA kit (Amersham Pharmacia Biotech Ltd., Buckinghamshire, UK), respectively. Venous blood samples for measurement were obtained through a 20 G indwelling needle inserted in the large forearm vein without venous occlusion. Plasma concentrations of both thromboxane B₂ and leukotriene C₄ gradually increased during exercise, and then reached to peak just after exercise and returned to baseline 30 minutes after exercise (Fig. 3).

These findings suggest that these constrictor mediators might, in part, play a role in the exercise-induced bronchoconstriction in this case. We therefore started treatment with a thromboxane A₂ synthesis inhibitor (400 mg/day of ozagrel, Ono Inc, Tokyo, Japan) and a leukotriene receptor antagonist (450 mg/day of pranlukast, Ono Inc, Tokyo, Japan). Bronchodilator drugs were excluded, and amlodipine and allopurinol were continued in same doses during the study. After treatment for 2 weeks, dyspnoea on effort decreased, % predicted FEV₁ at resting condition improved slightly from 74% to 81%, and percentage decrease in FEV₁ after exercise improved from 32.5% to

Fig. 1. Oxygen saturation measured from arterial blood gas sampling and heart rate at rest, during and after a bicycle ergometer exercise. In the present case, the oxygen saturation decreased during and especially after exercise. SaO₂: oxygen saturation, HR: heart rate, Ex: exercise.

Fig. 2. Krypton-81m ventilation and 99m-Tc-MAA perfusion scintigraphic images at rest and after exercise before treatment. Ventilation and perfusion images were normal at rest, but regional ventilation abnormalities were found after exercise.

Fig. 3. Plasma concentrations of thromboxane B_2 (TXB_2) and leukotriene C_4 (LTC_4) at rest, during and after a bicycle ergometer exercise. In the present case, plasma concentrations of TXB_2 and LTC_4 markedly increased with exercise.

Fig. 4. Krypton-81m ventilation scintigraphic images at rest and after exercise after 2 weeks treatment. The ventilation abnormalities after exercise improved after treatment, though the resting scintigraphies before and after treatment were similar.

13.3% (Table I). The exercise-induced abnormal ventilation detected with krypton-81m scintigraphy before treatment also improved after treatment with the combination of ozagrel and pranlukast, although the resting ventilation scintigraphies before and after treatment were similar (Fig. 4). The patient's exercise-induced hypoxaemia was ameliorated. Since leaving the hospital, the patient has been doing well for the past 3 years.

Discussion

In this case, krypton-81m ventilation scintigraphy was useful to evaluate the effectiveness of treatment of exercise-induced asthma with the combination of a thromboxane synthesis inhibitor and a leukotriene receptor antagonist. There are several previous reports on the changes in krypton-81m ventilation scintigram in asthmatic patients after exercise;^{12,13} however, no reports have been written about changes after treatment with bronchoconstrictor mediator antagonists. Although respiratory function test is useful to diagnose exercise-induced asthma and to evaluate

treatment, scintigraphy can visibly reveal the changes of regional ventilation, and furthermore could be useful when the patient is unable to cooperate with respiratory function test. Exercise-induced asthma was described by Floyer et al¹⁵ as early as the 17th century; however, the exact mechanism causing exercise-induced asthma has not yet been fully elucidated. Recently, the release of bronchoconstrictor mediators, such as leukotrienes and thromboxane resulting from changes in airway temperature and osmolality, has been postulated to cause exercise-induced asthma.⁷⁻¹⁰ In the present case, the symptoms and clinical findings improved after treatment with the combination of a thromboxane A_2 synthesis inhibitor and a leukotriene receptor antagonist. This suggests that either thromboxane A_2 , leukotriene or both contributed to the induction of exercise-induced asthma in this case. The beneficial effect of ozagrel and pranlukast on exercise-induced asthma cannot be ascertained as these drugs were not used separately. Previous investigations have demonstrated that both thromboxane A_2 synthesis inhibitors and leukotriene receptor antagonists are useful in the treatment of exercise-induced asthma. Hoshino and Fukushima⁹ reported that OKY-046, which is the same as ozagrel, was effective in 7 out of 14 patients with exercise-induced asthma, and was associated with a significant drop in thromboxane B_2 after treatment. The effect of leukotriene receptor antagonists was first demonstrated using MK-571, which is a selective antagonist for leukotriene D_4 , by Manning et al.⁸ They showed in a double-blind, randomised and cross-over trial with MK-571 and a placebo that the maximal percentage decrease in FEV_1 after exercise was $25.2 \pm 3.5\%$ in subjects taking placebo and $9.2 \pm 2.5\%$ in subjects taking MK-571. Finnerty et al¹⁶ also reported similar results in 8 patients with exercise-induced asthma using another leukotriene D_4 receptor antagonist (ICI 204219). Pranlukast, which was used in the present case, has a blocking effect on leukotriene D_4 , C_4 and E_4 . However, the actual role of leukotriene C_4 or E_4 in exercise-induced asthma is still unclear. In the present case, the plasma concentration of leukotriene C_4 increased during exercise, but this is not consistent with a previous report⁹ in which Hoshino and Fukushima measured plasma leukotriene C_4 before, during and after exercise in patients with exercise-induced asthma and demonstrated that the plasma level of leukotriene C_4 showed no change after exercise. Smith et al¹⁰ reported that urinary leukotriene E_4 levels of patients with asthma showed no significant change in the 24 hours after exercise, while allergens significantly increased the level of urinary leukotriene E_4 by a mean of 4 times the baseline value. We cannot assess the reasons for the differences between our results and previous reports as ours is based on 1 case only. Localised increases in leukotriene D_4 , C_4 and E_4 in bronchoalveolar lavage fluid

have also been demonstrated in exercise-induced asthma.¹⁷ Taken together, these results suggest that pranlukast may have also played an important role in the improvement shown in our patient due to its blocking effects on leukotriene D₄, C₄ and E₄.

In summary, this case suggests that the combination therapy of a thromboxane A₂ synthesis inhibitor and a leukotriene receptor antagonist might be useful in providing relief for patients with exercise-induced asthma, and that krypton-81m lung ventilation scintigraphy could be a useful tool for evaluation of treatment.

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