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Effects of Pranlukast, a Cysteinyl Leukotriene Antagonist, on Bronchial Responsiveness to Methacholine in Aspirin-Intolerant Asthmatics Treated with Corticosteroids

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ABSTRACT

Cysteinyl leukotrienes (cysLTs) are considered to be the most important mediator involved in the pathogenesis of aspirin-intolerant asthma (AIA). However, the role of cysLTs in the baseline condition of the pathophysiology of AIA when not exposed to non-steroidal antiinflammatory drugs (NSAIDs) as well as that in the pathophysiology of aspirin-tolerant asthma remains to be elucidated. Therefore, we evaluated the effect of pranlukast, a potent, selective cysLT receptor antagonist, on bronchial responsiveness to methacholine, a non-specific stimulus, in 7 well-controlled aspirin-intolerant asthmatics receiving oral or inhaled corticosteroid treatment. Pranlukast was orally administered at a dose of 225 mg twice daily to all patients for 4 weeks, and the methacholine challenge test was performed before and after pranlukast treatment. The methacholine provocative concentration producing a 20% fall in forced expiratory volume in 1 second (PC_{20}-FEV_1) was calculated as an index of bronchial hyperresponsiveness (BHR). The geometric mean values of PC_{20}-FEV_1 significantly ($p = 0.028$) increased from 0.34 mg/dl to 0.61 mg/dl after pranlukast treatment. No significant differences were observed in the baseline values of forced vital capacity (FVC) or FEV_1 before and after pranlukast treatment. These findings suggest that antagonism of endogenous cysLT by pranlukast may be responsible for the improvement of BHR to methacholine.

Key words: *Pranlukast, Cysteinyl leukotriene, Bronchial responsiveness, Aspirin-intolerant asthma*

Approximately 10% of adult patients with bronchial asthma have aspirin-intolerant asthma (AIA), and a severe, life-threatening asthma attack can follow ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin[16]. Recent studies showed that the urinary concentration of leukotriene E_4 (LTE_4) increases after the oral or inhalation challenge of aspirin in patients with AIA, but not in patients with aspirin-tolerant asthma[3,10,11]. Treatment with anti-leukotriene drugs has been shown to prevent aspirin-or other NSAIDs-induced bronchoconstriction[5,9,17]. These observations suggest that cysteinyl leukotrienes (cysLTs) play an important role in the bronchoconstriction in AIA. However, the role of cysLTs in the baseline condition of the pathophysiology of AIA when not exposed to NSAIDs as well as their role in the pathophysiology of aspirin-tolerant asthma remain to be elucidated. Therefore, we evaluated the effect of pranlukast[14], a potent, selective cysLT receptor antagonist, on bronchial responsiveness to methacholine, a non-specific stimulus, in well-controlled aspirin-intolerant asthmatics with oral or inhaled corticosteroid treatment.

MATERIALS AND METHODS

The subjects consisted of 7 well-controlled AIA patients on corticosteroid treatment, who were diagnosed by sulpyrine challenge test or by a history of asthmatic attack induced by NSAIDs (Table 1). All the subjects were non-smokers. Informed consent was obtained from all patients after the purpose of the study was explained. These patients had been treated with medication without any modification (see Table 1) for 6 months before pranlukast treatment.

Pranlukast was orally administered at a dose of 225 mg twice daily to all patients for 4 weeks. Concomitant medication was continued without

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Table 1. Patient characteristics

Patient No.	Age (years)	Sex	Type	Severity	Complication	Treatment			
						BDP (μg/day)	Theo (mg/day)	β_2-agonist	PSL (mg/day)
1	62	F	Ext	Moderate	AR/CS/NP	600	—	I	—
2	58	F	Int	Severe	AR/CS/NP	400	600	I/O	5
3	50	F	Ext	Moderate	AR/CS/NP	—	400	I	5
4	53	M	Ext	Severe	CS	1200	800	I/O	2.5
5	27	M	Ext	Moderate	AR/CS/NP	300	400	I	—
6	65	F	Ext	Mild	CS/NP	100	400	I	—
7	66	F	Int	Severe	—	—	—	I	10

BDP: Beclomethasone dipropionate; Theo: Theophylline; PSL: prednisolone; F: Female; M: Male; Ext: Extrinsic asthma; Int: Intrinsic asthma; AR: Allergic rhinitis; CS: Chronic sinusitis; NP: Nasal polyp; I: Inhaled administration; O: Oral administration

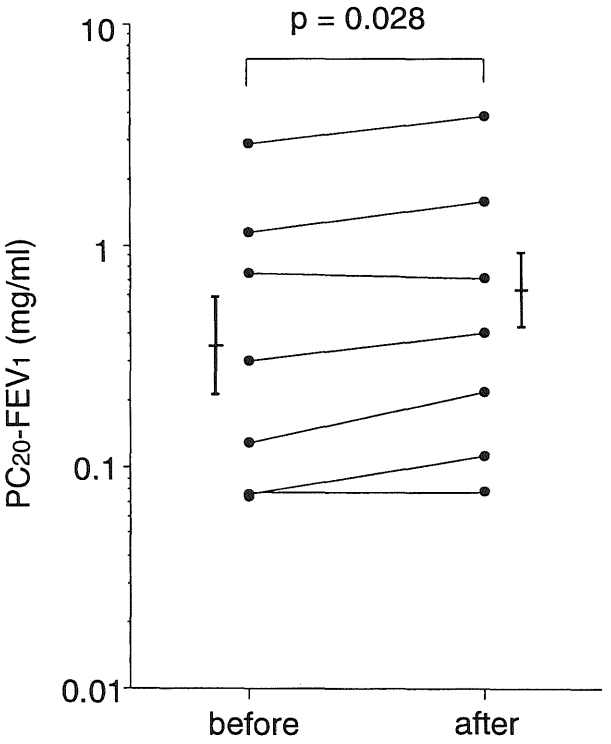

Fig. 1. Effect of oral administration of pranlukast on bronchial responsiveness to methacholine in aspirin-intolerant asthmatics undergoing oral or inhaled corticosteroid treatment. Group values are expressed as geometric means with geometric standard errors of the mean. PC_{20}-FEV_1 indicates the concentration of methacholine producing a 20% fall in forced expiratory volume in 1 second.

Table 2. Baseline FVC and FEV1 before and after pranlukast treatment

Item	Before	After
FVC, L	3.00 ± 0.48*	3.04 ± 0.48
FVC, %Pred	102.9 ± 5.4	104.9 ± 7.1
FEV1, L	2.06 ± 0.43	2.16 ± 0.45
FEV1, %Pred	82.8 ± 6.2	87.6 ± 7.0

* Data are expressed as means ± SEM.
FVC: Forced vital capacity; FVC, %Pred: Percentage of predicted of FVC; FEV_1: Forced expiratory volume in 1 second; FEV_1, %Pred: Percentage of predicted of FEV_1

any modification during the period of pranlukast treatment. The methacholine challenge test was performed before and after pranlukast treatment. Oral prednisolone or the other drugs including pranlukast were discontinued 26 or 14 hrs before the methacholine challenge test, respectively.

Bronchial responsiveness was evaluated by the methacholine challenge test as previously described[8,13]. Methacholine solutions of twofold-increasing concentrations were successively inhaled until a fall of 20% or more in forced expiratory volume in 1 second (FEV_1) was observed. The methacholine provocative concentration producing a 20% fall in FEV_1 (PC_{20}-FEV_1) was calculated. PC_{20}-FEV_1 was used as an index of bronchial hyperresponsiveness (BHR).

Methacholine PC_{20}-FEV_1 values were presented as geometric means with geometric standard errors of the mean (GSEM), and baseline values of forced vital capacity (FVC) or FEV_1 were presented as arithmetic means and standard errors of the mean (SEM).

RESULTS

The geometric mean values of PC_{20}-FEV_1 significantly increased from 0.34 (GSEM: 1.71) mg/ml to 0.61 (GSEM: 1.56) mg/ml after pranlukast treatment ($p = 0.028$, Wilcoxon signed-ranks test) (Fig. 1). No significant differences were observed in the baseline values of FVC or FEV_1 before and after pranlukast treatment (Table 2).

DISCUSSION

It has been observed that the baseline urinary excretion of LTE_4[3,10–12], expression of LTC_4 synthase in bronchial specimens[4,15], and sensitivity to inhalation of LTE_4[1,2] in patients with AIA are significantly higher than those in patients with aspirin-tolerant asthma. Thus, patients with AIA are considered to have both an increased basal production of cysLTs and an increased bronchial responsiveness to cysLTs in baseline condition even when not exposed to NSAIDs.

In the present study, pranlukast significantly improved baseline BHR to methacholine in well-controlled aspirin-intolerant asthmatics with oral or inhaled corticosteroid treatment, and the increase in PC_{20}-FEV_1 was 1.8 times. On the other hand, pranlukast did not affect baseline pulmonary function. Since all patients in the present study had been well controlled with the concomitant treatment, these findings suggest that antagonism of endogenous cysLT by pranlukast may be responsible for the improvement of BHR to methacholine.

Fujimura et al reported that oral pranlukast significantly improved baseline BHR to methacholine with an increase of 1.6 times in PC_{20}-FEV_1, accompanied by no improvement of baseline pulmonary function in mild stable asthmatics without inhaled or oral corticosteroid therapy[7]. Although the severity of the disease and profiles of concomitant treatment were different from those in the present study, the effect of pranlukast on BHR to methacholine in our patients was somewhat higher, suggesting the importance of cysLTs in the baseline condition of the pathophysiology of AIA. Recently, the administration of anti-leukotriene drugs such as the 5-lipoxygenase inhibitor zileuton[6] has been reported to be remarkably effective for the baseline treatment for AIA. This would support our hypothesis in the present study. Further strictly controlled studies such as a prospective, randomized, placebo-controlled, double-blind trial as well as studies of differences in the effect of anti-leukotriene drugs in patients with AIA and aspirin-tolerant asthma are necessary to clarify the precise role of cysLTs in the baseline condition in the pathophysiology of aspirin-intolerant or-tolerant asthma.

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