

The Effects of Inhaled Fluticasone and Pranlukast on Bronchial Hyperreactivity in Children with Asthma

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Background: Guidelines recommend inhaled corticosteroids and leukotriene modifiers as daily therapies to control asthma in children. However, few studies have compared the effects of these drugs on bronchial hyperreactivity in children with asthma.

Methods: The effects of inhaled fluticasone and pranlukast on bronchial hyperreactivity in 42 patients aged 7–15 years with mild persistent asthma (24 treated with inhaled fluticasone and 18 with pranlukast), who had experienced no asthma exacerbations after these treatments started, were studied. At the start of and after 6 and 18 months of treatment, bronchial hyperreactivity (PC20: provocative concentration of methacholine causing a 20% fall in FEV1) was assessed with methacholine.

Results: Geometric averages of PC20 in patients treated with inhaled fluticasone were 385.2 µg/mL at the start, 2271.8 µg/mL after 6 months, and 4181.0 µg/mL after 18 months of treatment, whereas those patients treated with pranlukast were 415.8 µg/mL, 792.2 µg/mL, and 2105.1 µg/mL, respectively. Both treatments induced significant improvements in PC20. The ΔPC20 values, expressed as doubling concentrations of PC20 after 6 and 18 months compared with that before treatment, were higher in patients treated with inhaled fluticasone than in those treated with pranlukast ($p < 0.05$ after both 6 and 18 months), whereas the ΔPC20 between PC20 after 18 months and that after 6 months of treatment did not differ between the two treatments.

Conclusions: These findings suggest that the therapeutic effects of inhaled fluticasone in increasing PC20 in patients with mild persistent asthma, who had experienced no asthma exacerbations after treatment commenced, were greater after 6 months of treatment, when compared with those of pranlukast, and then decreased.

Introduction

GUIDELINES RECOMMENDING MEDICATIONS FOR bronchial asthma, especially controller drugs, have changed recently, and the amounts of inhaled corticosteroids and leukotriene modifiers that are sold in Japan have increased.¹ These drugs are effective as controller drugs for asthma,^{2–6} and the numbers of patients dying of asthma exacerbations have decreased, while the amounts of these drugs sold in Japan have increased.¹ Inhaled corticosteroids and leukotriene modifiers are effective not only for preventing asthma exacerbations but also for improving pulmonary function^{2,4,5} and inflammatory biomarkers (exhaled nitric oxide)⁵ in patients with asthma. These drugs are also effective for decreasing bronchial hyperreactivity in such patients,^{7,8} but few studies have assessed and compared the effects on bronchial hyperreactivity in asthmatic children. In this study, we compared the effects of these drugs on bronchial hyperreactivity for

18 months in children with mild persistent asthma, who had experienced no asthma exacerbations after these treatments were started.

Materials and Methods

Sixty inhaled steroids and leukotriene modifiers naïve patients with mild persistent asthma^{9,10} aged 7–15 years with asthma symptoms once or twice a week were recruited to participate in this study. Inclusion criteria were (1) a diagnosis of allergic asthma for 1–2 years; (2) total serum IgE level between 100 and 2,000 IU/mL; and (3) more than 0.7 UA/mL of IgE RAST to at least one of the following allergens: *Dermatophagoides farine*, *Dermatophagoides pteronyssinus*, dog, or cat. Consecutive patients with mild persistent asthma diagnosed from November 2002 through January 2005 were recruited and divided alternately into an inhaled fluticasone (Flutide diskus inhalation powder) therapy group ($n = 30$)

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and a pranlukast (Onon dry syrup) therapy group ($n = 30$), who used these agents as daily controller medicines for 18 months. After these patients started treatment with one of these two drugs, they stopped taking other regular controller drugs (sodium cromoglycate, sustained released theophylline, and oral antiallergic compounds) (Table 1), and did not start treatment with long-acting inhaled β_2 -agonists and with other controller drugs, which contained inhaled corticosteroids for the patients treated with pranlukast and leukotriene modifiers for the patients treated with inhaled fluticasone, until the patients were excluded from the bronchial hyperactivity studies. The patients were given diaries in which they documented daily day- and night-time symptoms, disturbances of daily activity, and rescue bronchodilator use (rapid-acting inhaled β_2 -agonists and short-acting oral β_2 -agonists). Compliance with medications was assessed by examining prescription intervals and by checking the inhaled fluticasone device (Flutide diskus) for traces of fluticasone.

During the course of this study (from 1 to 18 months after treatment with these drugs had started), we defined patients reporting no asthma exacerbations as non-asthma-exacerbation patients (42 patients: 24 patients treated with inhaled fluticasone and 18 patients with pranlukast). Because 6 patients treated with inhaled fluticasone and 12 patients treated with pranlukast showed asthma exacerbations, which would influence bronchial hyperactivity in patients with asthma, and because these patients needed to take other above-mentioned controller drugs to prevent their further asthma exacerbations, we excluded these patients from the bronchial hyperactivity studies. There was no statistical difference between the two treatment groups in the number of patients excluded because of asthma exacerbations (χ^2 test, $p = 0.091$), and 42 non-asthma-exacerbation patients were recruited for bronchial hyperactivity studies.

We did not use placebo controls because the purpose of this study was to compare and differentiate the effects of inhaled fluticasone and pranlukast on bronchial hyperactivity in patients who showed good responses to these

drugs and who had experienced no asthma exacerbations after these treatments started.

Table 1 shows the backgrounds of non-asthma-exacerbation patients. These patients were treated with only inhaled fluticasone or pranlukast as controller medicines, and the dose of inhaled fluticasone (100–200 $\mu\text{g}/\text{day}$, 3.6–7.8 $\mu\text{g}/\text{kg}/\text{day}$, according to Japanese pediatric guideline for the treatment and management of asthma 2002 [JPGL2002]¹¹) or of pranlukast (7 $\text{mg}/\text{kg}/\text{day}$, according to JPGL2002¹¹) in each patient was not changed. At the start of treatment with these two controller drugs and at 6 and 18 months after the start of treatment, bronchial hyperactivity was assessed with methacholine. Bronchial hyperactivity was estimated with the concentration of methacholine that caused a 20% decrease in forced expiratory volume in 1 s (FEV1) (provocative concentration of methacholine causing a 20% fall in FEV1 [PC20]).¹²

The PC20 data were compared among before and after 6 and 18 months of treatment, and changes in PC20 (ΔPC20) after inhaled fluticasone or pranlukast treatment with respect to the pretreatment value and after 6 months of treatment value are expressed as the dose shift (in doubling concentrations) with the following formula: $\log_2(\text{PC20 after 6 or 18 months of treatment}) - \log_2(\text{PC20 before treatment})$ and $\log_2(\text{PC20 after 18 months of treatment}) - \log_2(\text{PC20 after 6 months of treatment})$.

Statistical analyses were performed with the Mann-Whitney U-test and Wilcoxon's signed-rank test.

The study protocol was approved by the ethics committee of the Hiroshima-Nishi Medical Center, and informed consent was obtained from the parents of each patient.

Results

Figure 1 shows the changes of PC20 in patients treated with inhaled fluticasone or with pranlukast.

Geometric averages of PC20 in patients treated with inhaled fluticasone were 385.2 $\mu\text{g}/\text{mL}$ at the start of treatment, 2271.8 $\mu\text{g}/\text{mL}$ after 6 months of treatment, and 4181.0 $\mu\text{g}/\text{mL}$

TABLE 1. PATIENT DEMOGRAPHIC FEATURES AND BASELINE CHARACTERISTICS

	<i>Inhaled fluticasone</i>	<i>Pranlukast</i>
Age, years, median (range)	12 (8–15)	11 (7–15)
Sex, n (%)		
Boys	15 (62.5)	10 (55.6)
Girls	9 (37.5)	8 (44.4)
History of other allergic disorders*, n (%)	20 (83.3)	14 (77.8)
Serum total IgE, IU/mL, median (range)	452 (182–1245)	531 (155–1578)
Controller drugs in 6 months before this study**, n (%)		
Sodium cromoglycate	15 (62.5)	9 (50.0)
Sustained released theophylline	18 (75.0)	12 (66.6)
Oral antiallergic compounds (repirinast)	2 (8.3)	1 (5.6)
Height, cm, median (range)	135 (108–171)	136 (108–168)
FEV1, % of predicted, median (range)	82.8 (49.5–105.2)	84.5 (65.5–109.4)
Bronchial hyperactivity to methacholine (PC20) before treatment, $\mu\text{g}/\text{mL}$, geometric average (range)	385 (37–3619)	416 (98–1924)

*History of other allergic disorders was indicated by patients' reports.

**These drugs were stopped after this study commenced.

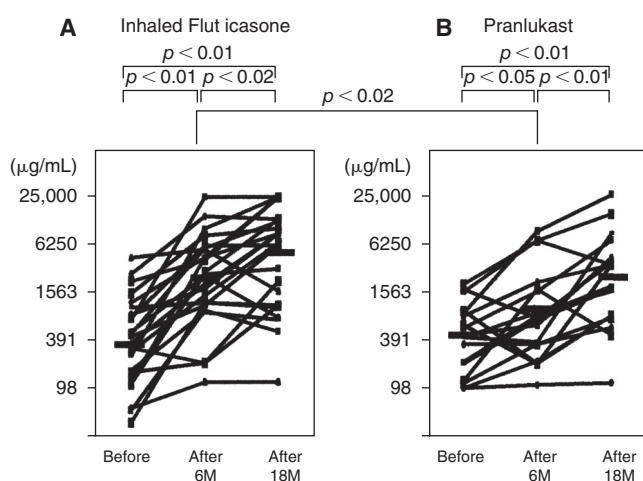


FIG. 1. Changes of provocative concentration of methacholine causing a 20% fall in FEV1 (PC20) in children with mild persistent asthma who had experienced no asthma exacerbations after starting treatment with inhaled fluticasone or pranlukast. (A) PC20 in children treated with inhaled fluticasone. (B) PC20 in children treated with pranlukast. —: Geometric average. Statistical analyses were performed with Wilcoxon's signed-rank test using PC20 values before treatment, and those after 6 and 18 months of treatment with each medicine. The Mann-Whitney U-test was used to compare the PC20 values of the two drugs before treatment and after 6 and 18 months of treatment.

after 18 months of treatment, whereas the geometric averages of PC20 in those patients treated with pranlukast were 415.8 $\mu\text{g/mL}$, 792.2 $\mu\text{g/mL}$, and 2105.1 $\mu\text{g/mL}$, respectively. Both treatments produced significant increases in PC20. After 6 months of treatment, PC20 in patients treated with inhaled fluticasone was higher than that in patients treated with pranlukast ($p < 0.02$), whereas PC20s in the two treatment groups did not differ significantly after 18 months of treatment.

Figure 2 shows ΔPC20 expressed as doubling concentrations from the beginning of treatment. Both treatments improved ΔPC20 significantly between 6 months and 18 months, and improvements in ΔPC20 after 6 months and 18 months were significantly greater with inhaled fluticasone than with pranlukast.

Figure 3 shows ΔPC20 expressed as doubling concentrations between PC20 before treatment and after 6 months of treatment and between after 6 months of treatment and after 18 months of treatment, and ΔPC20 in patients treated with inhaled fluticasone between PC20 before treatment and after 6 months of treatment were higher than those between after 6 months of treatment and after 18 months of treatment. After 18 months of treatment, ΔPC20 expressed as doubling concentrations from the data of PC20 after 6 months of treatments did not differ between the two treatments.

Discussion

Recently, asthma has been considered to be a disease characterized by bronchial hyperresponsiveness and inflammation throughout the bronchial tree,¹³ and airway

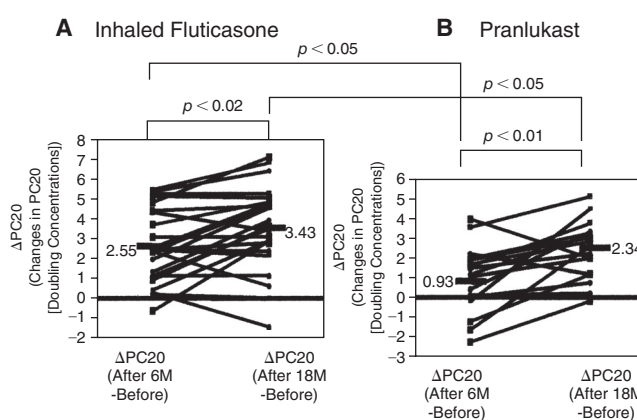


FIG. 2. Changes in PC20 (doubling concentrations) (ΔPC20) from before treatment during 18 months of treatment. ΔPC20 (After 6M-Before or After 18M-Before) = $\log_2(\text{PC20 after 6 months or 18 months treatments}) - \log_2(\text{PC20 before treatment})$. —: Average.

inflammation, remodeling, and bronchial hyperresponsiveness are believed to be interrelated.¹⁴

Anti-inflammatory drugs, especially inhaled corticosteroids and, to a lesser extent, leukotriene modifiers are recommended as effective controller medicines in the guidelines,^{9-11,15,16} and many children with asthma have been treated with these drugs. In GINA 2002 guideline,⁹ which was the most recent GINA guideline when this study was started, inhaled corticosteroids are recommended as daily controller medications for patients with mild to severe persistent asthma, whereas leukotriene modifiers are recommended as optional treatments for children with mild or moderate persistent asthma and as plus one choice of daily controller medicine for children with severe persistent asthma who have been treated with high-dose of inhaled corticosteroids.⁹ GINA 2006 guideline^{10,15} also recommends inhaled corticosteroids as initial controller treatments for patients of all ages, and recommends leukotriene modifiers as optional treatments or add-on treatments. In NAEPP Expert Panel Report 3,¹⁶ inhaled corticosteroids are the preferred drug for patients with mild to severe persistent asthma, and leukotriene modifiers are recommended as one of alternative drug for children with mild persistent asthma.

Many studies have shown that inhaled corticosteroids are more effective than leukotriene modifiers not only for controlling asthma symptoms, but also for improving pulmonary function and inflammatory biomarkers (exhaled nitric oxide) in adults and children.^{2,4-6} Although conventional and easy to perform measures of asthma control, such as Peak expiratory flow (PEF) and forced expiratory volume in 1 second (FEV1), along with asthma symptoms and reliever use, provide little or no information on the underlying inflammation process,¹³ and longitudinal bronchial hypersensitivity testings may reflect both airway inflammation and remodeling,¹⁴ few studies have compared the effects of these drugs on bronchial hyperreactivity in children.

In this study, despite many excluded patients, we demonstrated that in children with mild persistent asthma, who were treated with inhaled fluticasone or pranlukast and did not have any further asthma exacerbations after these

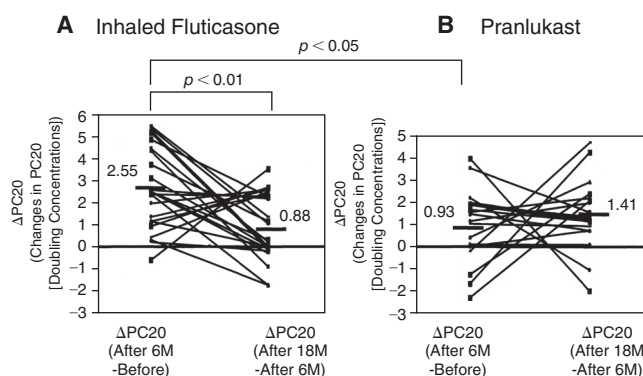


FIG. 3. Changes in PC20 (doubling concentrations) (Δ PC20) between before treatment and after 6 months of treatment, and between after 6 months of treatment and 18 months of treatment. Δ PC20 (After 6M-Before) = $\log_2(\text{PC20 after 6 months treatment}) - \log_2(\text{PC20 before treatment})$. Δ PC20 (After 18M-After 6M) = $\log_2(\text{PC20 after 18 months treatment}) - \log_2(\text{PC20 after 6 months treatment})$. —: Average.

treatments started, bronchial hyperreactivity assessed with methacholine (PC20) decreased significantly after 6 months and 18 months of treatment, compared with before treatment. We also showed that, after 6 months, PC20 in patients treated with inhaled fluticasone was higher than that in patients treated with pranlukast, whereas, after 18 months, PC20 did not differ between these two treatment groups. Further, we demonstrated that Δ PC20 after 6 months and 18 months compared to before treatment were higher in patients treated with inhaled fluticasone than in those treated with pranlukast, whereas Δ PC20 between PC20 after 18 months of treatment and that after 6 months of treatment did not differ between patients treated with inhaled fluticasone and those treated with pranlukast.

Our bronchial hyperreactivity findings after 6 months of treatment were similar to those of Riccioni et al.,⁸ showing that after 8 weeks of treatment with zafirlukast or budesonide, bronchial hyperreactivity (provocative dose of methacholine causing a 20% fall in FEV1 [PD20]) in patients with mild persistent asthma was relieved significantly by either treatment, when longitudinally compared with baseline values. However, Riccioni et al. did not directly compare the effects on PD20 between these two medications after 8 weeks of treatment, and did not investigate the effects on PD20 of longer-term treatment with these two drugs.

Boulet et al.¹⁷ have demonstrated that patients with recently diagnosed mild asthma and those with long-standing mild asthma show similar degrees of airway inflammation and subepithelial fibrosis and similar degrees of improvement in airway hyperresponsiveness after 8 weeks of treatment with high-dose inhaled corticosteroids, and that once asthma becomes symptomatic, airway responsiveness cannot be normalized in most patients over such a treatment period, even with a high dose of inhaled corticosteroids. These airway response data are similar to our inhaled corticosteroids data, which show that, after 6 months and 18 months of treatment, PC20 in most patients cannot be normalized.

Our Δ PC20 data agree with the data that show that inhaled corticosteroids are more effective than leukotriene

modifiers for improving pulmonary function in patients with asthma;^{2,4,5} our Δ PC20 data between 6 months and 18 months may suggest that the effects of inhaled corticosteroids are greater after 6 months of treatments and then decreased, to be similar to those of leukotriene modifiers.

Recent papers on asthma pathophysiology have reviewed current concepts of airway inflammation with an emphasis on the epithelium, smooth muscle dysfunction, and airway remodeling, which includes cellular proliferation, increased matrix protein deposition, basement membrane thickening, and angiogenesis.^{17–19} The detection of airway remodeling in subsets of asthma is difficult, and there is still no clinically useful biomarker.¹⁸ However, a selected panel of cytokines, growth factors, exhaled nitric oxide, and possible radiographic imaging may assist clinicians in detecting and providing targeting therapy for airway remodeling;¹⁸ unfortunately, we did not investigate these variables in this study. Future therapeutic strategies may involve these targets and synergistic approaches,¹⁹ especially with anti-IgE therapy (omalizumab) in preventing remodeling^{18,20} and in reducing airway hyperresponsiveness,²¹ because omalizumab has a serum-free IgE-reducing effect, inhaled corticosteroid-saving effects, and further anti-inflammatory activity compared with budesonide.^{18,20} Despite the effectiveness of inhaled corticosteroids, there is a continuing reluctance to use these agents, especially in younger patients.²⁰

In conclusion, despite many excluded patients, the small study size, and the limitation of the study design, which did not include an airway inflammation and remodeling study, the results of this study (as a pilot study) suggest that the therapeutic advantages for bronchial hyperactivity (Δ PC20 expressed as doubling concentrations of PC20 between before and after treatment) in children with mild persistent asthma who experienced no asthma exacerbations after being treated with inhaled fluticasone continued for 18 months, compared with those Δ PC20s in children treated with pranlukast. Also, up to 18 months of treatment, the advantages regarding PC20 and Δ PC20 in children with asthma treated with inhaled fluticasone might decrease, and Δ PC20 between 6 and 18 months of treatment showed no differences between inhaled fluticasone and pranlukast.

Author Disclosure Statement

No competing financial interests exist in this manuscript.

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