Efficacy and Tolerability of Salmeterol/Fluticasone Propionate versus Fluticasone Propionate in Asthma Patients: A Randomized, Double-blind Study

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Background: A combination of salmeterol and fluticasone propionate (SAL/FP) has been shown to be effective in the treatment of asthma. We compared the efficacy and tolerability of SAL/FP (50/250 μg) with fluticasone propionate (FP) 250 μg administrated twice daily for 2 weeks in treating patients with mild to moderate asthma.

Methods: This was a randomized, double-blind study in adult patients with symptomatic asthma that was not controlled by 1000 μg/d inhaled corticosteroids (ICS) alone. 48 asthmatics were randomized to receive 2 inhalations of SAL/FP 50/250 μg bis in die (BID) or 2 inhalations of FP 250 μg BID, both delivered via Accuhaler device, for 2 weeks. The primary objective was the mean change from baseline in the mean morning peak expiratory flow (PEF) over the two week period. Other parameters included lung function, daily asthma symptom scores, evening PEF, percentage of days free of rescue medication use and daily rescue medication use. Tolerability was assessed by adverse events spontaneously elicited at clinic visits.

Results: 46 patients provided evaluable efficacy for analysis. The morning PEF improved significantly throughout the two weeks of treatment compared with baseline in the SAL/FP group. Mean morning PEF was 23.0 L/min higher in SAL/FP group than in FP group ($p = 0.013$). The change of forced expiratory volume in one second (FEV_1) from baseline was greater in SAL/FP group compared to FP group ($p = 0.048$). There were similar effects on day-time and night-time symptom scores, percentage symptom free days and nights and usage of salbutamol. 70.8% of the patients receiving SAL/FP were satisfied with the treatment, while only 26.1% of patients receiving FP alone were ($p = 0.020$). No death or acute exacerbation occurred.

Conclusion: SAL/FP 50/250 μg was safe and effective, and had a high level of patient satisfaction resulting in significantly greater increases in morning PEF and FEV1 compared to the use of FP 250 μg alone.

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Key words: asthma, salmeterol/fluticasone propionate, peak expiratory flow, fluticasone propionate, lung function

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Asthma is an airway inflammation characterised by eosinophilia, mast cell infiltration, and activation of T-helper (Th) 2 cells, associated with bronchoconstriction and increased airway responsiveness.[1,2] Initial approaches to treat asthma emphasized the relief of bronchoconstriction with bronchodilators, particularly β_2-adrenergic agonists, but the discovery of airway inflammation as an important pathophysiological component of asthma has led to the use of inhaled corticosteroids as the mainstay of asthma therapy.[3] Since no medication can treat all aspects of the disease, most asthmatic patients require a combination of therapies. Of the combinations available, treatment with an inhaled steroid and a long-acting β_2-agonist is logical since the drugs have different modes of action which are complementary.[4] The inhaled steroid controls inflammation and the inhaled β_2-agonist controls symptoms and produces significant increases in morning and evening peak expiratory flow (PEF). Moreover international guidelines recommend that a long-acting β_2-agonist be used with antiinflammatory medications, with inhaled steroids being considered the most effective.[5]

A combination product of salmeterol and fluticasone propionate has been developed and shown to be effective and well accepted in both children and adults.[6-8] It is simple, reliable and easy to use. Inhalation is the preferred route of administration of anti-asthma drugs as a minimal dose of medication is applied topically to the target organ, reducing systemic exposure and side effects. Long acting β_2-agonists may improve symptoms that occur despite optimal use of steroids in mild to moderate asthma. The addition of a long-acting β_2-agonist may also reduce the need for high doses of inhaled steroids and the convenience of a combination of two therapies in a single device may enhance patient compliance. This study compared the efficacy and safety of a combination of salmeterol 50 μg and fluticasone propionate 250 μg in a single Accuhaler with that of fluticasone (FP) 250 μg via an Accuhaler twice daily in treating patients with asthma.

METHODS

Study design

This was a randomized, double-blind, parallel-group study. The trial took place between August 26, 2000 and October 24, 2000. The study design is summarized in Fig. 1. Patients fulfilled the entry criteria at Visit 1 if they continued to take their usual inhaled corticosteroids at a daily dose of up to 1000 μg of beclomethasone diproprionate or budesonide and still had night or day time symptoms. Patients were given salbutamol to be used as required basis, while all other rescue medication was stopped. After the 1 week run-in period, all patients who satisfied the entry criteria for the treatment period discontinued their usual inhaled steroid, replaced it with the study medication, and continued to use salbutamol as required basis. Eligible patients were randomized to receive either salmeterol/fluticasone propionate (Seretide 50/250 μg, twice daily) via an Accuhaler or fluticasone 250 μg (twice daily) via an Accuhaler. Patients stopped the study medication at the end of the 2 week treatment period (Visit 3), and the investigator was allowed to prescribe any other appropriate asthma medication. Depending on the investigator's discretion, patients returned for an optional follow-up Visit 4.

Patient disposition

Fifty-three patients were enrolled in the study. Five patients who were enrolled but not randomized were not included in the efficacy analysis. Two did not fulfill the inclusion criteria after the run-in period and three withdrew during the run-in period for personal reasons. Fig. 2 is an overview of the disposition of the patient population for the run-in and randomization phases. Forty-eight patients were randomized to the double-blind (treatment) phase, 24 in the Seretide 50/250 μg group, and 24 in the fluticasone 250 μg group. Two patients in fluticasone group did not complete the 2-week treatment period because of adverse events. One had a ureteral stone with severe pain and the other experienced acute exacerbation resulting from an upper respiratory tract infection. Of the 48 patients entering the treatment phase of the study, 47 patients (intent-to-treat population) had evaluable efficacy data on case report forms (24 in the Seretide group and 23 in the fluticasone group); 46 patients provided evaluable efficacy data on daily record cards (24 in the Seretide group and 22 in the Fluticasone group).

Primary and secondary objectives

To compare the efficacy of Seretide Accuhaler

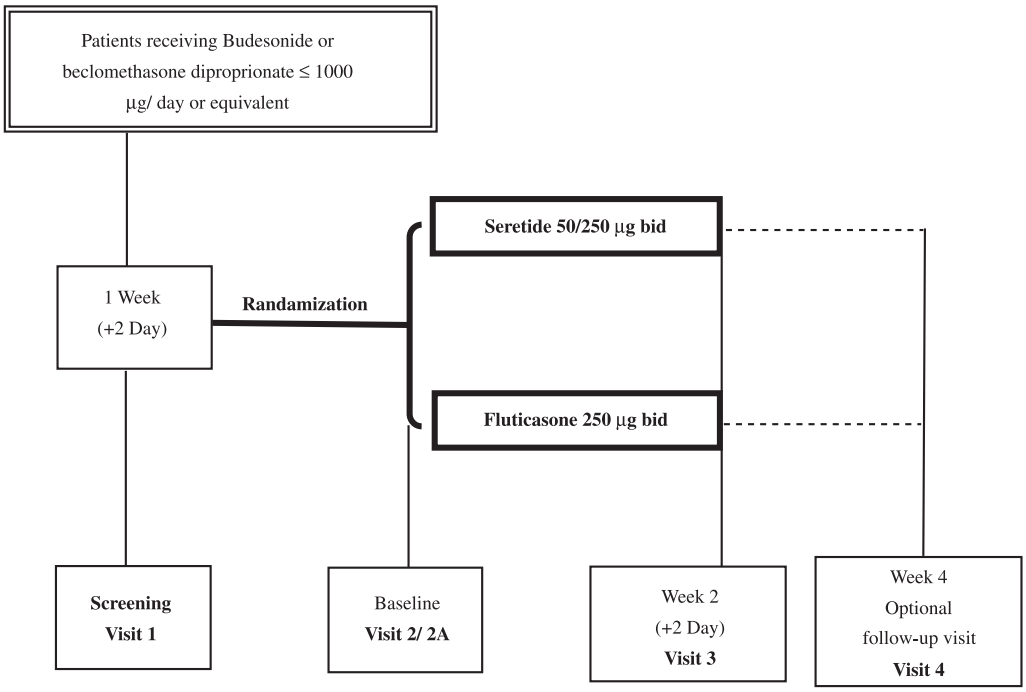

Fig. 1 Study design.

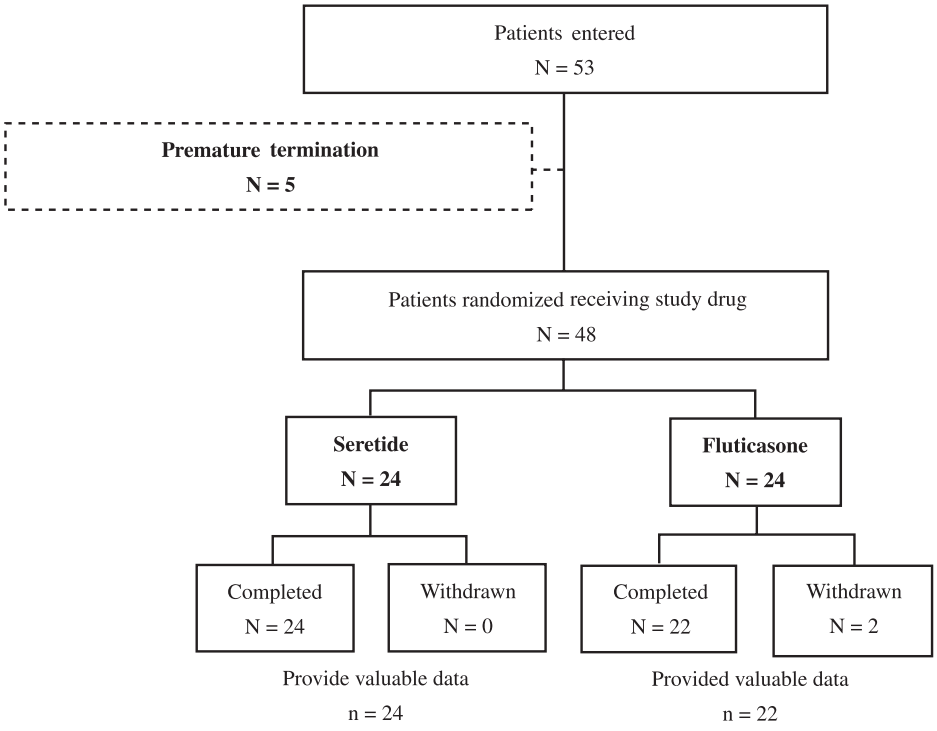

Fig. 2 Flow chart of patient disposition.

(50/250 μg) twice daily with fluticasone 250 μg twice daily in treating patients with reversible airway obstruction, the primary efficacy variable was the mean morning PEF over the two treatment weeks. The secondary efficacy measurements were the mean evening PEF, usage of salbutamol rescue medication, day and night time symptom scores, the forced expiratory volume in one second (FEV_1) measured at each clinic visit, safety and tolerability.

Patient papulation

Fifty-three patients with asthma who had been treated previously for at least two weeks prior to Visit 1 with a daily dose of beclomethasone diproprionate or budesonide up to 1000 μg were recruited. Asthma was defined according to American Thoracic Society criteria, as a ≥ 15% improvement in FEV_1 after inhalation of fenoterol (400 μg).[9] Patients with obstructive airway diseases such as chronic obstructive pulmonary disease or bronchiectasis, were excluded. Their FEV_1 was ≥ 50% and ≤ 80% of the predicted normal value at visit 1 or 2 on any day between these visits. Patients did not take any oral, parenteral or depot corticosteroids for at least 4 weeks prior to Visit 1. They also did not take a long-acting β_2-agonist or slow-release bronchodilator for at least 2 weeks prior to Visit 1. A woman was eligible to enter and participate in the study if she had no childbearing potential. Patients with a lower respiratory tract infection or an acute exacerbation requiring hospitalization within four weeks before entry were excluded. None of the patients had a serious uncontrolled systemic disease, including serious cardiac or psychological disorders. The study protocol was reviewed and approved by the Institutional Review Board of Chang Gung Memorial Hospital (No. 89-07) and subjects were given informed consent.

Daily records

Patients received daily record cards to complete from Visit 1 to 3. Patients brought the completed daily record cards with them to each subsequent visit. Patients began recording on this card on the morning of the day after their first visit. Daily records included morning and evening PEF, rescue salbutamol usage, and day and night time symptom scores.

Morning and evening peak expiratory flow (PEF)

Patients measured their PEF while standing using a peak flow meter every morning on awakening and every evening. All PEF measurements were made before taking the study medication or rescue salbutamol. Three measurements of the PEF were taken and recorded in the patient's notes and the highest was used in the analysis. If patients had used salbutamol within six hours, they documented its use on the daily record card.

Rescue ventolin usage

Patients recorded the number of occasions they had used salbutamol every morning (for any use during the night) and every evening (for any use during the day).

Day and night time symptom score

Day time symptoms were scored as follows: 0 = no symptoms during the day; 1 = symptoms for one short period (less than 30 minutes) during the day; 2 = symptoms for the two or more short periods during the day; 3 = symptoms for most of the day (more than 6 hours) that did not affect normal daily activity; 4 = symptoms for most of the day that did affect normal daily activity; 5 = symptoms so severe that they affected school work and normal daily activity. Night time symptoms were scored as follows: 0 = No symptoms during the night; 1 = symptoms causing awakening once during the night or early awakening; 2 = symptoms causing awakening twice or more during the night (including early awakening); 3 = symptoms causing the patient to be awake most of the night; 4 = symptoms so severe the patient did not sleep.

Pulmonary function test

At visits 1, 2/2A and 3 the highest of three technically acceptable measurements of the FEV_1 were recorded. The FEV_1 measurements were made using the same spirometer throughout the study and recordings were made in the morning as close as possible to 12 hours after the last dose of the study medication and at the same time of the day at each of the visits.

Patients' satisfaction rating and physician's assessment

At the end of treatment, the patients were asked to rate their overall satisfaction (very satisfied, satisfied, neutral, dissatisfied, very dissatisfied) with the treatment of asthma with the trial medication. The physician's assessment was also to ask the overall satisfaction rating (very satisfied, satisfied, neutral, dissatisfied, very dissatisfied).

Statistical analysis

Data are expressed by mean ± SD. Patient data: including sex, age, height, weight, FEV1 and reversibility of a bronchodilator test were summarized with descriptive statistics. We used Prism 5 software for data analysis. Fisher's exact test (qualitative data) or analysis of variance (quantitative data) was employed to test the homogeneity of the treatment groups. Comparability of treatment groups at baseline with respect to FEV_1, and morning and evening PEF were carried out using analysis of variance (ANOVA).

RESULTS

A total of 53 patients (64% men) from 19 to 75 years old (mean age 48.7 years) was entered into the study. Table 1 summarizes the baseline characteristics of the 47 patients in the intention-to-treat population. There were no significant differences in gender, age, body height or lung function between the Seretide and fluticasone groups (Table 1).

Table 1. Baseline Characteristics of the Patients

	Seretide (n = 24)	Fluticasone (n = 23)	*p* value
Age, years	49.8 ± 16.2	47.1 ± 16.8	0.766
Height, cm	162.7 ± 8.3	162.1 ± 10.2	0.571
Weight, kg	65.3 ± 14.3	62.8 ± 9.9	0.496
Lung function, FEV_1			
Before ventolin, L	1.9 ± 0.4	1.9 ± 0.4	0.900
Predicted value, %	68.3 ± 12.0	67.8 ± 12.0	0.888
After ventolin, L	2.2 ± 0.3	2.2 ± 0.3	0.866
Reversibility, %	15.5 ± 9.8	17.4 ± 9.6	0.504
Morning PEF, L/min	390.4 ± 94.3	375.7 ± 130.4	0.564
Evening PEF, L/min	398.3 ± 98.0	371.7 ± 123.1	0.416

Abbreviations: FEV_1: forced expiratory volume in one second; L: liter; PEF: peak expiratory flow. Data are expressed as mean ± SD.

Morning and evening peak expiratory flow (PEF)

One patient who received fluticasone experienced acute exacerbation and did not complete daily record of morning and evening PEF. Only 46 patients provided evaluable data for the following analysis of morning and evening PEF, and pulmonary function. The immediate treatment effects of Seretide indicated that the morning PEFs increased significantly over the first week compared with baseline (Fig. 3A). The mean morning PEF (mean PEF over seven days) at baseline was 396.3 ± 97.6 L/min for the Seretide group and 369.8 ± 125.6 L/min for the fluticasone group. During the first week of treatment, the mean difference in the morning PEF change above baseline between the two treatment groups was 23.0 L/min (Seretide group significantly higher than the fluticasone group; $p = 0.010$, 95% confidence interval (CI) 5.8 L/min to 40.2 L/min). Over the entire treatment period, the mean difference in the PEF (mean PEF over seven days) between the two treatment groups was 60.3 L/min (95% CI 13.4 L/min to 107.1 L/min). Within the Seretide group, the morning PEF improved significantly throughout the two weeks of treatment compared with baseline and the mean change from baseline was 35.1 L/min (95% CI 23.6 L/min to 46.7 L/min). Over the two weeks of treatment, the difference between the two treatment groups for the increment above baseline for the mean morning PEF was 22.3 L/min (Seretide group significantly higher than Fluticasone group; $p = 0.013$, 95% CI 5.0 L/min to 39.6 L/min) (Fig. 4A).

We also found the immediate treatment effect of Seretide on the evening PEF over the first week (Fig. 3B). Over the entire treatment period, the difference in the mean PEF between the two treatment groups was 51.0 L/min (95% CI 5.37 L/min to 96.7 L/min). Within the Seretide group, the evening PEF improved significantly throughout the two weeks of treatment compared with baseline and the mean change from baseline was 30.9 L/min (95% CI 19.7 L/min to 42.1 L/min). Over the two weeks of treatment, the difference between the two treatment

groups for the increase in mean evening PEF between groups was 16.9 L/min (Seretide group significantly higher than fluticasone group; $p = 0.048$, 95% CI 0.2 L/min to 33.6 L/min) (Fig. 4B).

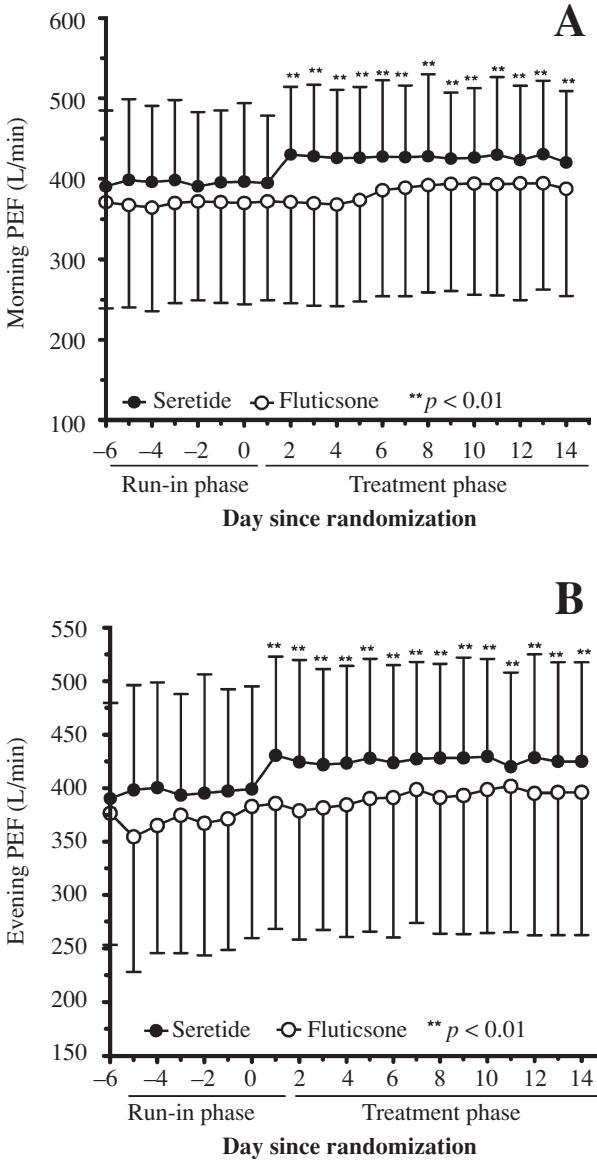

Fig. 3 Daily mean morning peak expiratory flow (PEF) (A) and evening PEF (B) for the run-in phase and treatment period. In the Seretride group (●, n = 24), both morning PEF and evening PEF improved significantly throughout the two weeks of treatment compared with baseline. However, the morning PEF and evening PEF did not show any significant changes in the fluticasone group (○, n = 22). Data are expressed as mean ± SD. $^{**}p < 0.01$ is compared with the baseline of the treatment phase (day 0).

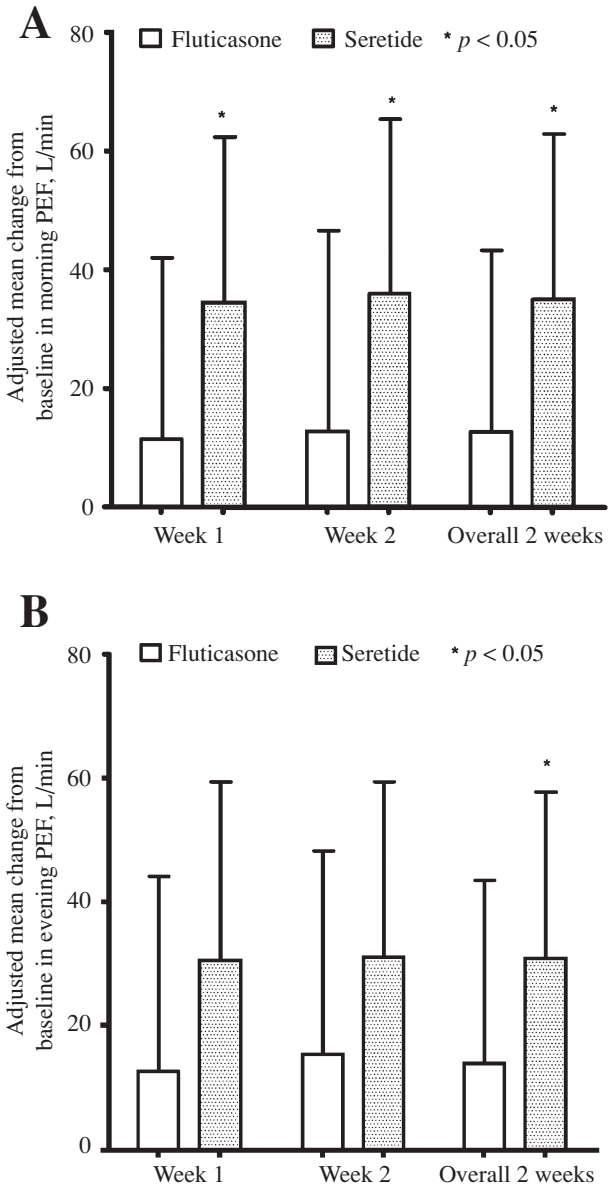

Fig. 4 Mean change in morning PEF (A) and evening PEF (B) from baseline to each week and over the entire treatment period. In the Seretide group, the morning PEF improved significantly throughout the two weeks of treatment (A) compared with the fluticasone group. Only the evening PEF over the two weeks of treatment in the Seretide group was significantly higher than that in the fluticasone group. Data are expressed as mean ± SD. $^{*}p < 0.05$ compared with that of the corresponding fluticasone group.

Pulmonary function

The subjects who were treated with Seretide had a significantly improved mean FEV_1 of 0.14 L (95% C.I.: 0.06 L to 0.22 L, $p = 0.037$) before salbutamol use after 2 weeks of treatment compared with baseline (Fig. 5). The difference in the increment of FEV_1 (before salbutamol) between the two treatment groups was 0.12 L (95% C.I. 0.01 L to 0.23 L). The results indicated that after 2 weeks, patients treated with Seretide had a significantly improved FEV_1 before salbutamol compared with patients treated with fluticasone. The mean reversibility at baseline was 15.5 ± 6.9% for the Seretide group and 17.4 ± 9.4% for the fluticasone group. Patients treated with Seretide had the reversibility significantly decreased compared with patients treated with Fluticasone throughout the 2-week treatment period ($p < 0.001$) (Fig. 6).

Asthma symptom scores

The day-time and night-time asthma symptom scores are summarized by week in Table 2. No statistically significant differences between groups were found for either score. The percentages of "symptom free days" during the assigned time intervals were compared between groups at pre- and post-treatment. The results indicated that there was no significant difference between the two groups at either time interval (Table 2).

Use of rescue medicine

Night-time usage of salbutamol is summarized by week in Table 3. Initially, the percentage of patients with night-time usage of salbutamol and mean percentage of nights using salbutamol were significantly higher in the Seretide group than the fluticasone group (Table 3). At week 2, the percentages of patients who used salbutamol significantly decreased from 50.0% to 16.7% ($p = 0.018$) in the Seretide group. At any point, patients in the fluticasone group had trends of better asthma control in terms of rescue medicine usage, however there was no significant change in the fluticasone group, which may have been due to the small case number. The mean percentages of nights of salbutamol use decreased from 25.7% (baseline) to 20.6% (over the treatment period) in the Seretide group and increased from 9.9% to 14.5% in the fluticasone group, with no statistical difference over the treatment period between groups.

Patients' satisfaction rating and physician's assessment

At the end of treatment, the patients were asked to rate their overall satisfaction (very satisfied, satisfied, neutral, dissatisfied, very dissatisfied) with the

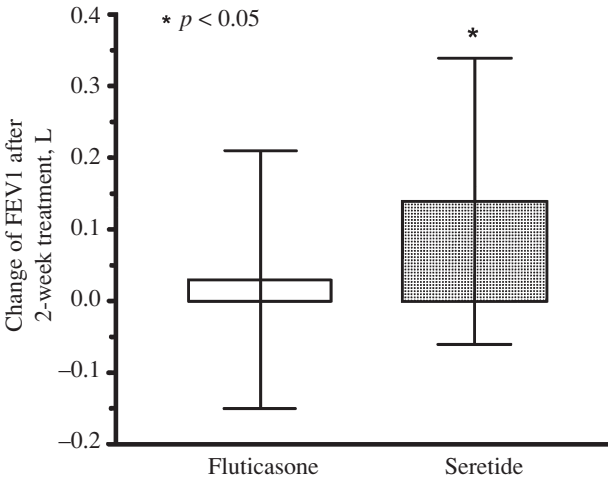

Fig. 5 Forced expiratory volume in one second (FEV1) after 2 weeks of treatment compared with baseline was significantly increased in the Seretide group (hatch bar, n = 24) compared with the fluticasone group (blank bar, n = 22). The data are expressed as mean ± SD. *$p < 0.05$ compared with the fluticasone group.

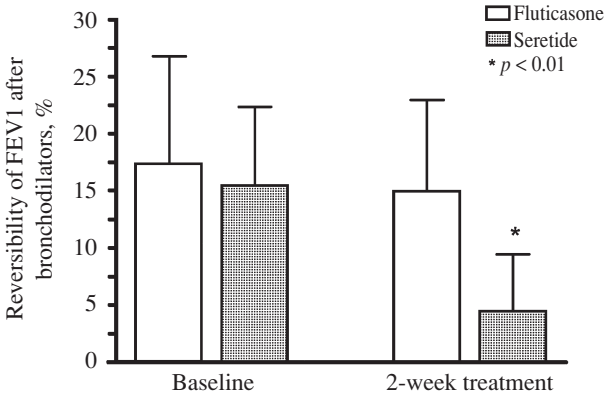

Fig. 6 Patients treated with Seretide (hatch bar, n = 24) had decreased bronchodilator reversibility compared with patients treated with fluticasone (blank bar, n = 22) throughout the 2-week treatment period. The data are expressed as mean ± SD. *$p < 0.05$ compared with the corresponding fluticasone group.

Table 2. Day and Night Time Symptom Scores

		Seretide (n = 24)	*p* value*		Fluticasone (N = 23)	*p* value*	*p* value
Day time symptom	No.			No.			
Mean percentage of symptom free days during the time interval							
Baseline	24	75.9 ± 31.1	0.354	23	72.3 ± 36.9	0.770	0.901
Week 1	24	83.9 ± 27.1		20	78.1 ± 34.2		0.578
Week 2	24	89.6 ± 25.4		18	91.7 ± 24.4		0.969
Overall 2 weeks	24	86.6 ± 25.1		20	80.9 ± 32.6		0.569
Mean symptom score during the time interval							
Baseline	24	0.3 ± 0.5	0.027	23	0.4 ± 0.7	0.153	0.786
Week 1	24	0.2 ± 0.3		20	0.3 ± 0.4		0.587
Week 2	24	0.1 ± 0.3		18	0.1 ± 0.3		0.968
Overall 2 weeks	24	0.2 ± 0.3		20	0.2 ± 0.4		0.534
Night time symptom							
Mean percentage of symptom free days during the time interval							
Baseline	24	84.1 ± 26.4	0.120	23	78.8 ± 36.3	0.072	0.638
Week 1	24	81.6 ± 28.4		20	92.5 ± 14.6		0.198
Week 2	24	91.2 ± 22.7		18	91.7 ± 25.7		0.506
Overall 2 weeks	24	85.8 ± 24.6		20	91.5 ± 18.1		0.289
Mean symptom score during the time interval							
Baseline	24	0.2 ± 0.3	0.241	23	0.3 ± 0.7	0.192	0.674
Week 1	24	0.2 ± 0.3		20	0.1 ± 0.2		0.199
Week 2	24	0.1 ± 0.3		18	0.1 ± 0.2		0.469
Overall 2 weeks	24	0.2 ± 0.3		20	0.1 ± 0.2		0.258

*: Repeated measures ANOVA was performed for mean night time or daytime symptom scores from baseline, week 1 and week 2 in each group. Wilcoxon rank sum test was used for the mean percentage of days using salbutamol between treatment groups.

trial medication. The results are demonstrated in Table 4. More than 70% of patients in the Seretide group and 26% of patients in the fluticasone group had a rating of satisfied or better. The physician's assessment rating was statistically significantly different between groups ($p = 0.020$) (Table 4). More patients were satisfied in the Seretide group than in the fluticasone group.

Safety

Forty-eight patients who received any amount of study drug were included in the analysis of safety. Four patients (Seretide: 1; Fluticasone: 3) reported a total of five adverse events. One adverse event of esophagitis was assessed by the investigator as fluticasone related. Two patients treated with fluticasone did not complete the study because of adverse events, one with a ureteral stone and another with an upper respiratory tract infection. Therefore, the investigator felt that these events were not related to the study medication and concluded it was incidental. No deaths, hospitalizations or acute exacerbations occurred during this study.

DISCUSSION

This study was a randomized, double-blind, parallel-group study comparing the tolerability and efficacy of a combination of salmeterol 50 μg and fluticasone propionate 250 μg in a single Accuhaler, (Seretide 50/250 μg) with fluticsone 250 μg administrated twice daily in the management of patients with mild to moderate asthma. Within the Seretide group, the morning and evening PEF were significantly

Table 3. Night Time Usage of Salbutamol

		Seretide (n = 24)	*p* value†		Fluticasone (n = 23)	*p* value†	*p* value
Number of subject use ventolin during the time interval, N (%)							
Baseline	No	12 (50.0%)			19 (82.6%)		0.030
	Yes	12 (50.0%)			4 (17.4%)		
Week 1	No	15 (62.5%)			14 (70.0%)		0.752
	Yes	9 (37.5%)			6 (30.0%)		
Week 2	No	20 (83.3%)			16 (88.9%)		0.685
	Yes	4 (16.7%)*			2 (11.1%)		
Overall 2 weeks	No	15 (62.5%)			14 (70.0%)		0.752
	Yes	9 (37.5%)			6 (30.0%)		
Mean percentage of days using ventolin during the time interval							
Baseline	24	25.7 ± 33.0	0.195	23	9.9 ± 25.9	0.910	0.028
Week 1	24	23.1 ± 36.6		20	15.0 ± 28.0		0.530
Week 2	24	16.7 ± 38.1		18	9.3 ± 27.5		0.572
Overall 2 weeks	24	20.6 ± 36.2		20	14.5 ± 29.1		0.586

Fisher's exact test was performed for number of subjects using salbutamol between treatment groups. *$p = 0.018$ compared to the baseline of Seretide group.

Wilcoxon rank sum test was used for mean percentage of days using salbutamol between treatment groups.

†: Repeated measures ANOVA was performed for mean percentage of days using salbutamol from baseline, week 1and week 2 in each group.

Table 4. Summary of the Patients' Satisfication of Treatment

	Seretide n = 24	Fluticasone n = 23	*p* value
Very satisfied (%)	5 (20.8)	1 (4.4)	0.020
Satisfied (%)	12 (50.0)	5 (21.7)	
Neutral (%)	7 (29.2)	16 (69.6)	
Dissatisfied (%)	0 (0.0)	1 (4.4)	
Very dissatisfied (%)	0 (0.0)	0 (0.0)	

p value: test of the general association using Mantel-Haenszel statistics.

improved immediately and throughout the treatment period. During the first week of treatment, the difference in the morning PEF change above baseline between the two treatment groups was 23.0 L/min (Seretide group significantly higher than fluticasone group; $p = 0.010$). Thus, Seretide was superior to fluticasone in terms of the morning and evening PEF after treatment.

Asthma may be regarded as a disease with three interrelated components, airway inflammation, smooth muscle dysfunction, and airway remodeling, the first two of which can be effectively treated with corticosteroids and long-acting β2-agonists (LABAs), respectively.[10-12] Despite the lack of effective treatment for airway remodeling, it is believed that a better outcome can be achieved by appropriate and early management of asthma. Studies show that Seretide achieves better asthma control than therapy with increased doses of inhaled corticosteroids (ICS) alone.[13] This is likely attributable to the complementary actions of corticosteroids and LABAs, including the differential inhibition of the inflammatory cascade and mutual activation of their respective receptors. Previous study has also shown that the combined use of fluticasone propionate and salmeterol appears to be superior over either agent used alone in the inhibition of the proliferation of smooth muscle

cells.[14] The superior efficacy of the Seretide Accuhaler over fluticasone used alone was demonstrated in this study involving symptomatic asthma patients previously under inhaled corticosteroid treatment. In our study of primary efficacy variables, intention-to-treat analysis showed that at 1 and 2 weeks after randomization, significantly greater improvements from baseline in the morning and evening PEF were observed in patients receiving Seretide than in patients receiving fluticasone alone. The mean morning PEF, for instance, improved from baseline to the end of week 2 by 35.1 L/min in the Seretide group compared with 12.8 L/min in the fluticasone group ($p < 0.05$) (Fig. 4). The superiority of Seretide over fluticasone was evident as early as the first day of treatment and was maintained over the study period. After the first day of treatment with Seretide, the mean morning PEF, for example, increased by 33.7 L/min. In patients receiving fluticasone alone, however, an improvement of only 1.1 L/min was observed, significantly less than that among patients receiving Seretide ($p < 0.01$) (Fig. 4). The improvement in the mean morning PEF at week 2 was very similar to that in a meta- analysis which showed a mean morning PEF improvement of 22.4 L/min at three months in those who received added salmeterol compared with those treated with an increased dose of inhaled steroids.[6] Another study also reported an increase in the mean morning PEF over the first 2 weeks of 30.1 L/min in the fluticasone + salmeterol group which was higher than that in the fluticasone group (5.2 L/min).[15] Similar results were obtained for the evening PEF. Therefore, combination therapy with an ICS and LABA may have more efficacy in the management of chronic persistent asthma.

The mean FEV_1 change from baseline in the Seretide group over the 2-week treatment period was 0.14 L, which was significantly greater than the 0.03 L recorded in the fluticasone group (Fig. 4). These results are also compatible with the study by van Noord et al who reported an increase in FEV1 from baseline of 0.15 L, in the Seretide group, which was greater than 0.06 L in the fluticasone propionate group after four weeks of treatment.[15] Moreover, after 2 weeks of treatment, patients receiving Seretide had a bronchodilator-mediated FEV_1 reversibility reduction of 11.8%, which was significantly greater than the 1.8% reduction among patients receiving fluticasone alone (Fig. 6). This means that salmeterol has a persistent bronchodilator effect and attenuates the reversibility of airways with additional bronchodilators, such as salbutamol. Salmeterol produced significant increases in morning and evening PEF and reduced the need for additional short-acting bronchodilator treatment. Our results are in keeping with similar studies by Greening et al,[16] Woolcock et al,[17] and van Noord et al[15] who reported large groups of patients with mild to moderate asthma in whom the addition of salmeterol 50 μg twice daily was more effective at improving PEF, lung function and symptoms than increasing the dose of corticosteroids from 400 to 1000 μg daily. Therefore, Seretide may have a greater effect in decreasing bronchoconstriction compared with using fluticasone alone.

In our short 2 week study, the significant improvement in PEF and FEV1 might have been due merely to the effect of a LABA in the Seretide group. Although no parallel group using a LABA alone was used in this study, all other studies of 12-week treatment reported significant improvement in morning and evening PEF as well as FEV1 with Seretide compared with salmetrol alone. None reported significantly greater improvement with salmetrol alone.[18-20] There are several possible explanations for the superior efficacy of Seretide over fluticasone observed in our study or over salmetrol alone in other studies. LABAs may modulate neurotransmission and inhibit mast cell mediator release, enhancing the expression of corticosteroid receptors, and thereby potentiating the anti-inflammatory actions of ICS.[21] Furthermore, ICS are thought to protect against the loss of beta 2 receptors, and may therefore enhance the long-term benefits of beta-agonists.[7]

Although significantly higher percentages of symptom-free days and days free of rescue medication were achieved in the Seretide group, the overall percentages of symptom-free and rescue-free days in the FP group were also high. Therefore, in patients with mild to moderate asthma, taking regular maintenance doses of an ICS can be effective in improving symptoms and decreasing rescue medication. However, a combination of an ICS and a LABA may afford greater protection against the triggers of acute exacerbation by improving pulmonary function.[22] A longer trial is required to compare the differences in

symptom scores and acute exacerbation between patients using Seretide or fluticasone alone in the treatment of chronic asthma.

More than 70% of the patients receiving Seretide were satisfied with treatment, and no single case of dissatisfaction was reported. In comparison, only 26% of patients receiving fluticasone alone were satisfied with their treatment and one patient even reported dissatisfaction. During the study period, four patients reported adverse events. Among the three patients with adverse events in the fluticasone, only one case of mild esophagitis was believed to be related to the use of ICS. The remaining patient, from the Seretide group, reported palpitations and gastroesophageal reflux, both of which were mild. Basically, the use of Seretide is tolerable and safe in the treatment of chronic asthma.

This prospective study has several limitations. First, this study was conducted at a single medical center, and there may be patient population selection bias and referral patterns. Second, the sample size was too small, although our study was a randomized and double-blind trial. Third, a treatment period of 2 weeks for chronic asthma is too short to draw conclusions on safety and long-term side effects. We need a large group of patients and a longer treatment time to examine the effects of Seretide on long-term control of chronic asthma. Despite these limitations, this study provides data on the efficacy and tolerability of combination therapy in Taiwanese patients with mild to moderate asthma.

In conclusion, Seretide Accuhaler is safe and effective, with a high level of patient satisfaction for the regular treatment of asthma when use of a combination product (LABA + ICS) is indicated. In patients not adequately controlled with ICS and 'as needed' inhaled reliever therapy, Seretide is considered a more appropriate choice of pharmacologic treatment than the use of an ICS alone. Seretide 50/250 μg is well tolerated and safe in treating patients with asthma.

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氣喘病患使用 Salmeterol/Fluticasone Propionate 與 Fluticasone Propionate 的療效與耐受度比較：隨機雙盲研究

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背 景： 複方使用 salmeterol 與 fluticasone 的藥物 (SAL/FP combination) 已知在治療氣喘病人是具有療效的。本研究的目的在比較使肺泰準納乾粉吸入劑 (Seretide Accuhaler 50/250 μg) 與輔舒酮吸入劑 (fluticasone, Accuhaler 250 μg) 兩者在輕度至中度氣喘病患每日兩次使用兩週之後的療效和耐受性。

方 法： 本研究在成年的氣喘病患中篩選出接受每天 1000 μg 吸入性類固醇治療，而尚無法有效獲得控制的患者，進行隨機並雙盲性的研究。患者被隨機分配成兩個組別，各自接受使肺泰 (SAL/FP 50/250 μg) 與輔舒酮 (FP 250 μg) 早晚各一次，每次兩吸，持續兩週的治療。兩種藥劑同樣使用準納乾粉定量吸入器 (Accuhaler device)。研究主要指標在早晨尖峰呼氣流速值 (morning peak expiratory flow) 平均值在兩週後的平均變化值。其他比較的參數包括肺功能，每日氣喘症狀評分，傍晚尖峰呼氣流速值 (evening peak expiratory flow)，需要以及不需要使用發作急救用藥的天數，及兩者的百分比。藉著患者自述不良反應或門診時探問的方式評估治療的耐受性。

結 果： 48 位患者被隨機分配接受使肺泰與輔舒酮，兩週後在使肺泰組的早晨尖峰呼氣流速值比原本的基準值有明顯改善。兩組間早晨尖峰呼氣流速值平均值差異達到 23.0 L/min (p = 0.013)，傍晚尖峰呼氣流速值的比較也呈現類似結果，兩週後第一秒用力吐氣肺容積改善的變化在使肺泰組相較於輔舒酮組有明顯增加 (p = 0.048)。日間和夜間氣喘症狀評分，日間與夜間無發作症狀天數的百分比，以及泛得林定量噴霧劑的使用上，兩組病患無差異。70.8% 接受使肺泰治療的患者對治療感到滿意，輔舒酮治療的患者只有 26.1% 對治療感到滿意 (p = 0.020)。沒有患者死亡或急性發作住院。

結 論： 使肺泰治療用於氣喘病患與輔舒酮作比較，是較安全、有效，且病患滿意度高，其早晨尖峰呼氣流速值和第一秒用力吐氣肺容積也明顯改善。

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關鍵詞： 氣喘，salmeterol/fluticasone propionate，尖峰呼氣流速值，fluticasone propionate，肺功能

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