Peer reviewed article

Salmeterol/fluticasone propionate (50/250 µg) combination is superior to double dose fluticasone (500 µg) for the treatment of symptomatic moderate asthma

A prospective, double-blind trial

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Summary

Questions under study: if patients with asthma remain symptomatic in spite of chronic treatment with inhaled corticosteroids (ICS), increasing the ICS dosage or adding another drug to the treatment regimen are possible therapeutic alternatives. We compared the efficacy and safety of combined salmeterol fluticasone therapy (SFC, 50/250 µg twice daily) with twice the dose of fluticasone propionate (FP, 500 µg b.i.d.) in symptomatic asthmatics.

Methods: this prospective, double-blind study was conducted in 76 study centres. 365 symptomatic patients with moderate asthma aged >18 years and receiving ICS in a dose equivalent to 1,000 µg beclomethasone propionate per day were randomly assigned to receive either salmeterol xinafoate (50 µg) and fluticasone propionate (250 µg) in a single dry powder inhaler (Diskus®) or 500 µg FP twice daily. The primary efficacy endpoint was morning peak expiratory flow rate (PEFR). Secondary measurements included forced expiratory volume in 1 second (FEV_1), asthma symptom scores, and use of rescue medication.

Results: combined salmeterol fluticasone therapy resulted in significantly greater improvements in PEFR and symptom control than doubling the dose of FP. At week 12, morning PEFR had increased by 52 L/min from baseline in patients on SFC and by 36 L/min in subjects receiving FP. The adjusted difference between groups was 16.6 L/min (95% confidence interval, 1.1 to 32.0 L/min). In the SFC group, the percentage of symptom-free days increased from baseline by 49% of days as compared with 38% of days after FP (adjusted difference: 12.6% of days, 95% CI 4.0 to 20.7). Quality of life improved to a greater degree after SFC therapy, and patients regarded study drugs as superior to their previous asthma medication. Adverse event profiles were similar between groups.

Conclusions: the combination of salmeterol 50 µg and fluticasone 250 µg in a single dry powder inhaler was superior to twice the dose of FP (500 µg). It seems justified to add salmeterol rather than increasing the ICS dose if symptomatic asthmatics require supplementary therapy.

Key words: asthma; fluticasone; salmeterol; inhaled corticosteroids; lung function; quality of life; treatment

Introduction

Asthma is a chronic inflammatory disease of the bronchial mucosa with hyperreactivity and reversible bronchospasm secondary to certain stimuli [1]. Consequently, chronic anti-inflammatory treatment, usually with inhaled corticosteroids, is required for patients with persistent asthma. To alleviate acute bronchospasm, patients use inhaled short-acting bronchodilators, eg, beta-agonists or ipratropium bromide. Long-acting formulations of beta-agonists have been developed in the 1990ies which provide bronchodilatation for 8 to 12 hours after a single inhalation. A preparation combining the inhaled corticosteroid (ICS), fluticasone, and the long-acting beta agonist (LABA), salmeterol, was licensed for asthma treatment in 1998. This medication provides asthma control

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and relief of symptoms in a single inhaler, and the convenience of the combination product may improve patient adherence to the prescribed drug regimen [2].

Combined treatment with both ICS and LABA has been found in randomised controlled trials to be more effective than a higher dose of the inhaled corticosteroid [3, 4–6].

Evidence from basic research has accumulated indicating complementary modes of action of corticosteroids and long acting beta agonists. Three major hypotheses have been generated: 1, a direct effect of LABAs on inflammatory cells and production of inflammatory mediators, 2, an additive effect of both drugs on asthma-specific inflammatory processes, and 3, an effect of ICSs on β_2-receptor synthesis.

The present clinical trial was designed to study the efficacy and tolerability of the salmeterol fluticasone combination in comparison with doubling the dose of fluticasone in patients with moderate symptomatic asthma. Asthma symptoms, peak expiratory flow rates and lung function tests were regularly assessed during the 12 week treatment period. We also determined how patients and their physicians assessed the efficacy of treatment and how patients described their quality of life during treatment. The aim of the study was to determine whether combination therapy with salmeterol (50 µg) and fluticasone (250 µg) was superior to 500 µg fluticasone twice daily.

Patients and methods

Study design and ethical aspects

This was a multi-centre, randomised, double-blind trial comprising a 2-week screening period and a 12-week treatment period in which the twice daily administration of the combination product (250 µg fluticasone propionate plus 50 µg salmeterol xinafoate) was compared with that of 500 µg fluticasone. Patients from 76 study centres (private practices or outpatient clinics at hospitals) were admitted to the screening phase. There were five study visits: at start of screening (week –2), at randomisation / start of treatment (week 0), and at weeks 2, 6, and 12 of treatment (end of study). The study was conducted in accordance with the Declaration of Helsinki, the German Drug Law (Arzneimittelgesetz), and with Good Clinical Practice Guidelines as issued by the European Community. Approval from the ethics committee was obtained for each participating centre, and patients gave their written informed consent before entering the study.

Admission and exclusion criteria

Patients aged 18 to 70 years who had their asthma diagnosed at least 6 months before the screening visit were eligible for the screening phase of the study. The diagnosis was made according to the German asthma guidelines [7]. Admission was possible if the patient had asthma of moderate severity (ie, asthmatic symptoms less than once per day, but not more frequently than twice per week, during the daytime, or asthmatic symptoms at least twice per month, but less than once per week, at night time, a forced expiratory volume in 1 second, FEV_1, between 50% and 80% of predicted, and an increase in FEV_1 after 200 µg of inhaled salbutamol of at least 15% from baseline). Further entry criteria were: the patient was a non- or ex-smoker, and asthma had been treated with inhaled corticosteroids (beclomethasone dipropionate (BDP) or budesonide, 800 to 1000 µg per day, or fluticasone, 500 µg per day) for at least 3 months prior to the study. Treatment with theophylline, cholinergic drugs, or leukotrienes was permitted provided the dose was not changed during the trial.

Patients who had received previous therapy with inhaled long-acting beta agonists, oral beta-agonists, oral or parenteral corticosteroids during the preceding 4 weeks were excluded. Further exclusion criteria were: change of asthma medication, treatment with other study medication, respiratory tract infection or hospital stay due to respiratory problems during the preceding 4 weeks; inability of the patient to correctly administer study drugs; known allergy to components of the study medication; severe concomitant illness or other chronic respiratory disease (such as cystic fibrosis or interstitial fibrosis); and in women, inadequate contraception, pregnancy or lactation.

During the screening phase, patients recorded asthma symptoms and peak flow measurements in the diary cards (see below), while continuing their usual asthma medication. After two weeks, they returned for the second study visit to determine whether they had been symptomatic and were eligible for receiving study medication. At least one of the following criteria had to be met for inclusion into the treatment period: use of rescue medication on ≥7 of 14 days, OR total asthma symptom score ≥10 points (the sum of scores from 14 days and nights). Patients were not admitted to the treatment phase if entries into the diaries were incomplete and not considered reliable by the study physician, or if they had experienced a respiratory tract infection during the screening period.

Patient diaries and peak flow measurements

Patient diaries were used twice daily for the report of asthma symptoms, peak flow rates and use of salbutamol rescue medication. Daytime and night-time asthma symptoms were recorded on five-point scales according to the following classification: 1. daytime symptoms: 0 = no symptoms, 1 = symptoms for one short period during the day, 2 = symptoms for two or more short periods, which did not affect normal activity, 3 = frequent symptoms during the day, which did not affect normal activity, 4 = symptoms for most of the day which affected normal daily activity; 2. night-time symptoms: 0 = no symptoms, 1 = symptoms causing awakening once during the night, 2 = symptoms causing awakening twice or more, 3 = symptoms causing the patient to be awake most of the night, 4 = symptoms so severe that the patient did not sleep. Patients were taught how to use a mini-Wright peak-flow meter. They were asked to record throughout the study the best of three blows each morning and evening, before use of any medication. Patient diaries were collected at each study visit and replaced by new ones.

Respiratory function tests

Spirometric measures of pulmonary function were made at each clinic visit. Patients had to perform forced

expiratory manoeuvres while taking flow-volume measurements. Reference data from the European Commission for Coal and Steel (ECSC) related to sex and height were used as normal values [8].

Quality of life measurements

Health-related quality of life was assessed by means of an asthma-specific questionnaire, the asthma quality of life questionnaire [9]. The validated German version of this instrument was used. At the start and end of the treatment phase, patients answered questions on a scale from 1 (most severe impairment) to 7 (least impairment). The 32 items were grouped into four dimensions (asthma symptoms, physical activity, environment, and emotions), and a mean individual score could also be calculated.

Randomisation and study medication

Study medication was administered for twelve weeks. A computer generated randomisation code was used to allocate half of the patients to each of the two treatment legs. Randomisation was in balanced blocks of four with each centre allocated at least one block, and sequentially numbered, opaque, sealed envelopes were used for the procedure.

Patients were either treated with the combination product, fluticasone 250 µg plus salmeterol 50 µg (group SFC), or with fluticasone in a dose of 500 µg (group FP). Study treatment was provided in Diskus® powder inhalers. Each morning and evening, patients inhaled one dose from the powder inhalation device. Patients were asked to inhale salbutamol rescue medication if they developed acute asthmatic symptoms. This drug was provided in metered dose inhalers containing 300 puffs of 100 µg salbutamol. Use of rescue medication was recorded in the patient diaries.

End-points and required number of patients

The primary end-point of the study was morning peak expiratory flow rate (PEFR) from diary cards at week 12 compared with measurements obtained during the screening period. To identify a difference of 15 l/min between treatment groups with a power of 80% at an alpha level of 0.05, 174 patients with useable data per group were required assuming a standard deviation of morning PEFR of 50 l/min in both groups.

The secondary end-points, evening PEFR, asthma symptom score, percentage of symptom-free days/nights, and use of rescue medication were also recorded in patient diaries. Further secondary end-points were respiratory function tests obtained at clinic visits. Flow-volume manoeuvres were recorded to measure forced expiratory volume in one second, FEV_1, forced vital capacity, FVC, and peak expiratory flow, PEF. Asthma quality of life was assessed at the beginning and end of the study.

Drug Safety

Safety and tolerability of study medication was assessed by physical examination including oropharyngeal inspection, heart rate and blood pressure measurements and by adverse event reporting. Physicians judged the severity of each adverse event and its relationship to study medication.

Statistics

Primary and secondary end-points from diary cards were analysed by calculating the means of values recorded during the weeks preceding the respective visit. Values of week 12 represent the mean of diary card entries from the preceding 21 days, values for week 6 are from the preceding 14 days, and those of base-line from the last 7 days before randomisation. 95% confidence intervals were calculated for the difference between adjusted group means, with baseline value, age, sex and height as continuous covariates, and less than two years prior treatment with inhaled corticosteroids or prior treatment with fluticasone as binary covariates. The primary endpoint was also analysed according to the duration of prior treatment with inhaled corticosteroids or with theophylline. All statistical tests were two-sided at an alpha level of 0.05. 95% confidence intervals were calculated for adjusted differences. Unless mentioned otherwise, results are from the intention-to-treat (ITT) groups (see below) and are presented as means and standard deviations (or 95% confidence intervals). The ITT group consisted of those patients who inhaled at least one dose of study medication and had no critical protocol violation (eg, a missing diary from the screening period).

Results

Patient disposition and base-line characteristics

A total of 399 patients were recruited from 76 study centres (figure 1). After the 2-week screening period, 365 patients fulfilled randomisation criteria and received either the salmeterol fluticasone (50/250 µg) combination (group SFC) or fluticasone 500 µg bid (group FP). The 347 patients who inhaled study medication and had no critical protocol violation (e.g., a missing diary from the screening period) represent the intention-to-treat (ITT) group, of which 170 belonged to the SFC group. The per-protocol group consisted of 275 patients (138 from the SFC group) with complete results and no major protocol violation.

Demographic data, lung function and diary card results at randomisation

Table 1 shows demographic data, asthma symptoms and lung function test results at randomisation. Mean age of the 347 patients was 49.3 years, and 53.6% were female. The two treatment groups were comparable with respect to age, severity of asthma symptoms, or results of respiratory function tests. During the last seven days of the 2-week screening period, mean total asthma symptom score was 28 points (of a theoretical maximum of 56 during day and night), and only 17% of days were symptom-free. Accordingly, patients inhaled two to three puffs of salbutamol rescue medication each day. As required for inclusion of patients into the study, lung function showed considerable impairment, with decreased means for FEV_1 and peak

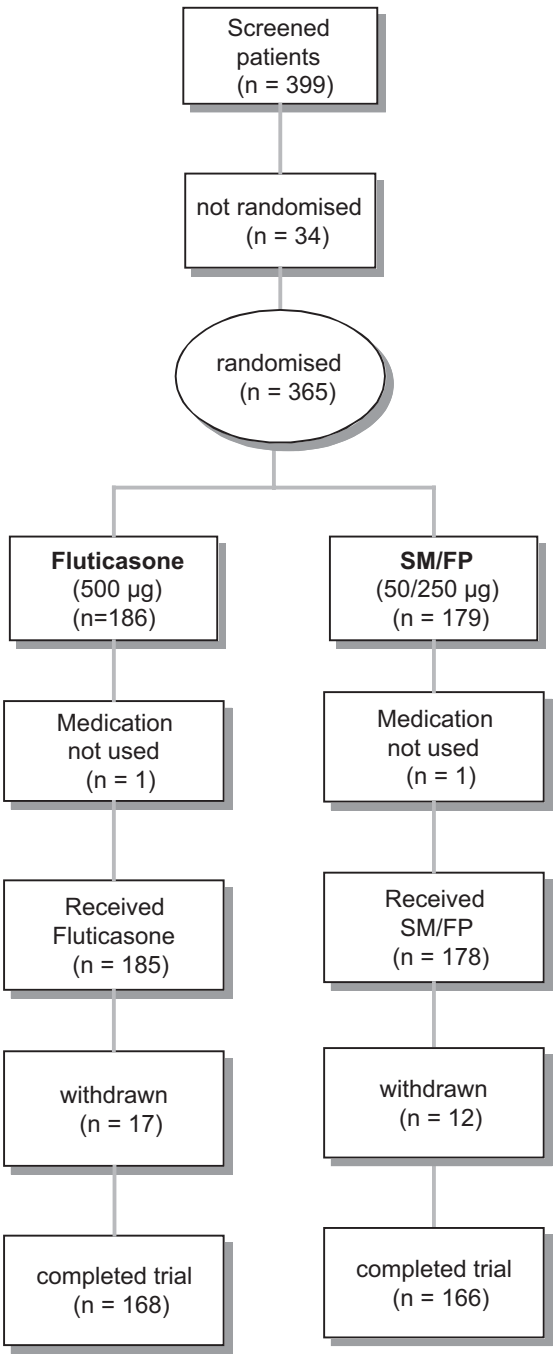

Figure 1

Patient disposition. SM/FP: salmeterol/fluticasone combination product.

flow compared to normal values (75% and 73% of predicted, respectively).

Efficacy

Morning peak expiratory flow rate

The primary end-point was morning PEFR as measured by patients throughout the study and reported in diary cards. Combined salmeterol fluticasone therapy was superior to double dose fluticasone with respect to the increase in morning peak expiratory flow rate (Table 2). A significant improvement was observed already after two weeks of therapy, when the salmeterol fluticasone combination group showed an increase of 37 l/min (or 7.8% of predicted) compared to base-line, and the fluticasone group had an elevation of 20 l/min (or 4.5% of predicted). Figure 2 shows morning and evening PEFR after 6 and 12 weeks compared to the screening period. Morning PEFR increased further during the study, so that differences of 19.6 l/min (6.8 to 32.4 l/min) and 16.6 l/min (1.1 to 32.0 l/min) between groups were observed at 6 and 12 weeks, respectively. In the per-protocol groups, morning PEFR improved by a mean of 48.4 l/min after 6 weeks and by 51.3 l/min after 12 weeks of SFC therapy, and the respective increases in the FP group were 29.9 and 32.9 l/min.

In another analysis, patients were grouped according to the duration of previous treatment with inhaled corticosteroids. Those patients who had received ICS for more than two years responded particularly well to salmeterol fluticasone therapy (+11.3% predicted, n = 88) compared with fluticasone (+5.2% predicted, n = 87) at week 12. Analysis of covariance revealed that concomitant theophylline therapy had no influence on the primary endpoint.

Diary card assessments

Results from diary cards for asthma symptoms and use of rescue medication at week 12 are given in Table 2. Both treatment groups improved compared to previous asthma therapy. Significantly better results were obtained after combined therapy with fluticasone and salmeterol than with double-dose fluticasone ($p < 0.05$). Adding salmeterol to fluticasone improved symptoms and increased the percentage of symptom-free days to a greater degree than doubling the ICS dosage.

Respiratory function tests

Pulmonary function tests improved in both treatment groups during the study (Table 3, Figure 3). FEV_1 increased by 12.3% of predicted after 12 weeks of SFC therapy and by 8.4% after fluticasone, respectively. No statistically significant differences were found between groups with respect to clinic lung function results.

Quality of life and patients' perspective of drug efficacy

At week 12, patients reported considerable improvements in asthma related quality of life. Means of all five test dimensions increased in both groups (Figure 4). Changes of more than 1 point (out of 7) were observed in the SFC group with respect to asthma symptoms and physical activity as well as for the mean score. The minimal important difference of this quality of life score has been reported to be 0.5 points [10].

Patients and investigators were asked to assess the efficacy of treatment on a five point scale. After 12 weeks, 82.4% of physicians assessed combined treatment and 72.3% fluticasone therapy as "excellent" or "good". Ratings from patients were comparably encouraging (81% in the SFC group and 74.0% in the FP group, respectively).

Patients were also asked to assess current therapy in comparison to the treatment they had received before study entry. Forty-four percent of SFC patients rated the overall efficacy of study

Table 1

Demographic data, respiratory function tests and diary card data at randomisation (means and standard deviations).

	Salmeterol/Fluticasone (50/250 µg) Combination (n = 170)	Fluticasone (500 µg) (n = 177)
Age (yrs)	49.8 (14.2)	48.9 (13.9)
% female	50.6	56.5
Asthma diagnosis		
1 to 5 years before entry	30.6	36.2
5 to 19 years before entry	24.1	14.7
Start of inhaled corticosteroids		
3 to 5 years before entry	24.7	18.6
>5 years before entry	26.5	30.5
FVC (% pred.)	87.2 (22.8)	88.1 (24.5)
FEV_1 (% pred.)	74.5 (19.3)	75.7 (20.2)
MEF25 (% pred.)	30.2 (22.7)	30.6 (18.2)
Peak expiratory flow rate (% pred.)	73.1 (26.0)	73.5 (24.8)
Mean morning PEFR (diary card, l/min)	318 (111)	316 (102)
Mean evening PEFR (diary card, l/min)	333 (110)	330 (105)
Sum of symptom scores (optimum: 0)	27.5 (17.3)	28.9 (17.9)
Percentage of symptom-free days (%)	17 (27)	16 (25)
Salbutamol rescue medication (puffs per day)	2.4 (1.8)	2.7 (2.4)

Table 2

Change in morning and evening peak expiratory flow rates, asthma symptoms, and use of rescue medication after 6 and 12 weeks of study medication in comparison to base-line at randomisation (means, standard deviations), and adjusted differences between groups (95% confidence intervals). The results are from analysis of co-variance with treatment as experimental factor and baseline values, age, sex, height, duration of preceding treatment with inhaled corticosteroids shorter than two years (yes/ no), fluticasone medication prior to the study (yes/no), and MEF_{50} less than 50% of predicted (yes/no) as co-variates.

	Change at 6 Weeks				Change at 12 Weeks			
	Salmeterol/ Fluticasone (50/250 µg) Combination	Fluticasone (500 µg)	Adjusted differences between groups (95% CI)	P value#	Salmeterol/ Fluticasone (50/250 µg) Combination	Fluticasone (500 µg)	Adjusted differences between groups (95% CI)	P value#
Morning PEFR (l/min)	+48 (63)	+30 (56)	19.6 (6.8; 32.4)	0.0027	+52 (76)	+36 (65)	16.6 (1.1; 32.0)	0.0356
Evening PEFR (l/min)	+44 (60)	+24 (57)	20.2 (7.7; 32.6)	0.0016	+ 46 (73)	+29 (65)	18.1 (3.1; 33.0)	0.0178
Symptom score	–1.2 (1.4)	–0.9 (1.4)	–0.4 (–0.65; –0.12)	0.0049	–1.5 (1.4)	–1.0 (1.5)	–0.5 (–0.78; –0.22)	0.0005
Percentage of symptom-free days (%)	+40 (39)	+29 (39)	12.8 (4.5; 21.0)	0.0025	+49 (38)	+38 (40)	12.6 (4.0; 20.7)	0.0038
Salbutamol use (puffs per day)	–1.4 (1.8)	–1.0 (1.9)	–0.5 (–0.85; –0.20)	0.0015	–1.6 (1.9)	–1.0 (2.2)	–0.84 (–1.13; –0.37)	0.0001

for the differences between treatment groups

drug as "much better" than their previous asthma medication, 41% as "better", 11% as "similar", and only 4% as "worse" than pre-trial medication. The percentages from the FP group were 34%, 45%, 14%, and 6%, respectively. As shown in Figure 5, patients assessed the study drug as an improvement in their daily treatment. The ease of use and safe handling of the Diskus® device were most frequently mentioned. Patients from the SFC group gave more positive ratings than those from the FP group, for example with respect to long-term symptom control and avoidance of asthma attacks.

Safety and Tolerability

Adverse events

A total of 92 patients experienced adverse events during the treatment phase of the study with similar frequencies in both groups (SFC: 26.3%, FP: 24.2%). The most common diagnosis was respiratory tract infection (12 in the SFC group and 25 in the FP group). Only few asthma exacerbations were observed during the twelve weeks treatment period: four in the fluticasone and one in the combination product group. There were 13 adverse drug reactions during salmeterol fluticasone treatment and 17 during fluticasone inhalation, of

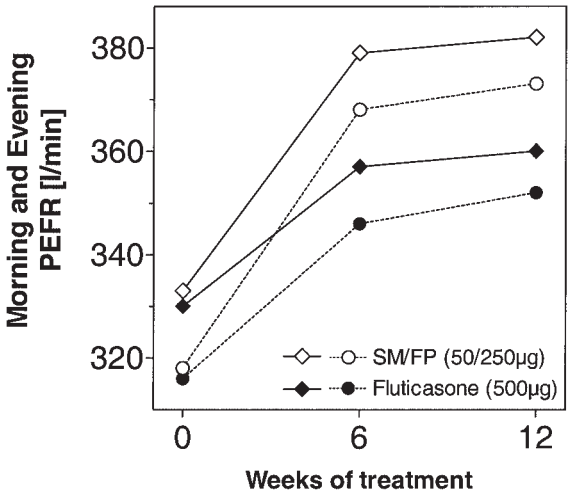

Figure 2

Mean morning (circles) and evening (squares) peak expiratory flow rates (l/min), as measured by patients during treatment.

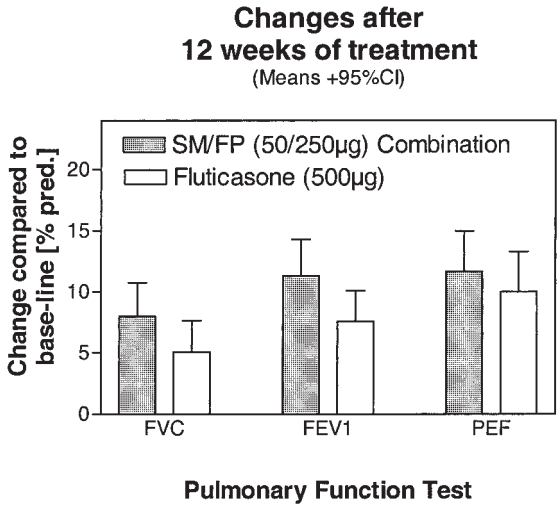

Figure 3

Spirometry results during treatment: Forced vital capacity, FVC, and forced expiratory volume in 1 second, FEV_1, expressed as percentages of the predicted value (means).

Table 3

Pulmonary function test results after 6 and 12 weeks of treatment (means and standard deviations in parentheses). There were no statistically significant differences between groups, as determined by analysis of co-variance.

	After 6 Weeks		After 12 Weeks	
	Salmeterol/ Fluticasone (50/250 µg) Combination (n = 170)	Fluticasone (500 µg) (n = 177)	Salmeterol/ Fluticasone (50/250 µg) Combination (n = 170)	Fluticasone (500 µg) (n = 177)
Forced vital capacity, FVC (% predicted)	94 (26)	91 (24)	95 (28)	93 (28)
Forced expiratory volume in 1 sec, FEV_1 (% pred.)	84 (24)	82 (22)	86 (26)	83 (24)
Peak expiratory flow rate, PEFR (% pred.)	83 (27)	81 (24)	84 (27)	83 (27)

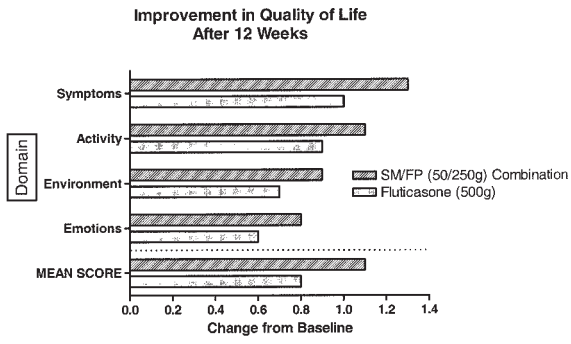

Figure 4

Improvement in quality of life.

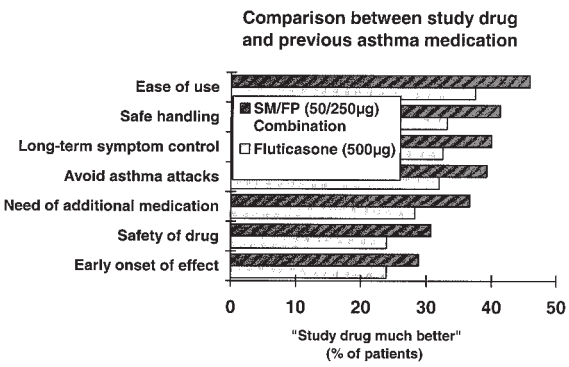

Figure 5

Patients' rating of study drugs in comparison to their previous asthma medication.

which the following occurred in more than one patient per group: dysphonia (3 in the SFC group and 3 in the FP group), moniliasis (1 vs 3), arrhythmia (0 vs 2), weight gain (2 vs 1), and speech disorder (2 vs 0). Forty-one events which were possibly or probably related to study drug were reported in 28 patients, of whom 13 received fluticasone.

Four serious adverse events (SAEs) were described: an arm fracture, nasal surgery, coronary artery disease, and asthma exacerbation. The latter was rated as possibly related to study drug (fluticasone) by the physician. Two unrelated SAEs were observed in the SFC group.

Heart rate and blood pressure

Systolic and diastolic blood pressure remained stable during treatment (from a mean of 130/80 mm Hg at week 0 to 129/79 mm Hg at week 12, respectively). Mean heart rate did not change throughout the study (change: –0.3/min in the SFC group and –0.9/min in group FP).

Discussion

Patients with asthma who are symptomatic while receiving anti-inflammatory therapy require supplementary medication. This double-blind, prospective trial shows that the combination of salmeterol xinafoate, a long-acting beta agonist, and fluticasone propionate, a potent inhaled corticosteroid, in a single dry powder inhaler (50/250 µg Diskus) is more effective in this situation than doubling the dose of fluticasone to 1000 µg per day.

According to current asthma guidelines two different treatment options are available if asthmatic patients remain symptomatic: adding another drug (eg, theophylline, a LABA or a leukotriene antagonist) to the treatment regimen or increasing the dose of inhaled corticosteroids [7, 11]. The present trial demonstrates that adding salmeterol provided more benefit than doubling the dose of fluticasone. Clinically relevant increases in morning PEFR were achieved in patients receiving double dose (500 µg) fluticasone twice daily as well as in patients inhaling a combination of salmeterol (50 µg) and fluticasone (250 µg). The frequency of asthma symptoms decreased, and patients had more symptom-free days and used less rescue medication with the salmeterol fluticasone combination product. When comparing the results of both groups, statistically significant differences in favour of the combination were present early in the study. Already after two weeks of treatment, morning PEFR had increased by 37 l/min in comparison to only 20 l/min in the double dose fluticasone group. Morning PEFR was chosen as primary end-point because the "morning dip" with unstable PEFR-values is characteristic for symptomatic asthma. For this reason this parameter has been used as a primary end-point in many clinical trials. In the present study, both spirometric and diary card peak flows improved by 11.7 percent of the predicted value after SFC, but spirometry PEF had a considerably larger standard deviation (21.5% of predicted) than diary PEF (15.6% of predicted), resulting in statistically insignificant changes in spirometry. Furthermore, diary card data represent individual means from multiple measurements performed by the patient during a one or two week period, whereas spirometry at a clinic visit is performed only at one time-point and requires optimal performance of patient, laboratory personnel and spirometry equipment. From 2 to 12 weeks in the present study, peak expiratory flow rates increased further and in parallel in both groups, so that a 16.6 l/min difference in morning PEFR between treatments was present at the end of the trial.

The magnitude of changes observed with combined salmeterol fluticasone therapy was comparable to that reported in previous studies. The phase III trial by Ind and co-workers comprised six months treatment with either fluticasone 1000 µg, fluticasone 500 µg or salmeterol 100 µg plus fluticasone 500 µg per day [6]. Morning peak expiratory flow rate improved by 48 l/min after six months of combined treatment and by 22 l/min after double dose fluticasone. The greatest increase was observed within the first month of treatment. Time without asthma symptoms increased significantly, and patients had 65% of days and 95% of nights free from symptoms after six months. In the present study, symptom-free days increased from 17% at base-line to 65% after 12 weeks of combined salmeterol fluticasone therapy and from 16% to 53% after fluticasone propionate.

A meta-analysis summarised the results of nine randomised clinical trials including 3685 patients with bronchial asthma symptomatic on inhaled steroids who received additional salmeterol or an increased dose of inhaled corticosteroids [12]. Asthma control was significantly better after adding salmeterol than after at least doubling the ICS dose: patients had 15% more days and 8% more nights without asthma symptoms and 20% fewer days which required the use of rescue medication. Likewise, improvement in lung function was more pronounced in the salmeterol group, with a 28 l/min larger increase of morning peak expiratory flow rate after six months of salmeterol plus inhaled steroid therapy than after increasing the inhaled steroid dose. A stronger effect of salmeterol plus inhaled steroid therapy was also seen with respect to the number and severity of asthma exacerbations, which are regarded as a marker for control of underlying inflammation [12]. Another recent literature review showed that the addition of salmeterol to low-dose fluticasone propionate provided better control of asthma than increasing the dose of fluticasone propionate [13]. Greater improvements in FEV_1, peak expiratory flow, and symptom control were achieved with combined treatment.

Regarding the prolonged administration of salmeterol, a long-term study demonstrated that its bronchodilator properties, as indicated by hyperresponsiveness to methacholine, were sustained over 52 weeks of treatment [14].

These results from clinical trials suggest that salmeterol and inhaled corticosteroids have a complementary role in the treatment of bronchial asthma. However, this was demonstrated only in

patients who continued to have asthmatic symptoms with moderate doses of inhaled corticosteroids. Researchers have presented experimental data regarding possible synergistic effects of these substances. The combination of salmeterol and low dose fluticasone reduced the number of airway mast cells and T-cells compared with the same dose of fluticasone and did not lead to increased airway inflammation [15]. Inhaled corticosteroids increased β_2-receptor synthesis in vivo at clinical doses by activating the β_2-receptor gene [16]. In the presence of salmeterol and fluticasone, the degree of translocation of the glucocorticoid receptor to the nucleus increased [17]. If patients are exposed to high doses of salbutamol, a down-regulation of β_2-receptors on circulating lymphocytes may occur, and this can be prevented by systemic steroids [18]. Furthermore, the number of cellular β_2-receptors increased after ICS therapy. Concerning inflammatory responses in the airways, steroids increase apoptosis (cell death) of eosinophils, and the potency of fluticasone to induce eosinophil apoptosis was increased 3–5 fold in the presence of salmeterol [19]. The release of the cytokine GM-CSF by human airway epithelial cells is inhibited by both steroids and LABAs. A combination of ICS and LABA had increased inhibitory activity over each drug alone [20]. Thus, recent advances in basic research support the hypothesis of a synergistic action of LABAs and inhaled corticosteroids.

In summary, the present trial demonstrated that administering salmeterol to asthmatic patients who have symptoms despite a daily dose of 1000 µg beclomethasone or 500 µg fluticasone resulted in greater asthma control, less need for rescue medication and better lung function than doubling the dose of fluticasone. This improvement was achieved without any additional safety concerns. Considering the possible adverse effects of long-term high-dose ICS treatment, it seems justified to add salmeterol rather than to increase the ICS dosage when supplementary therapy is required. For the convenience of the patient, combined therapy is available in a single dry powder inhaler. A decision as to whether the new treatment is adequate can be made early, since the effects of salmeterol are noticeable within two weeks.

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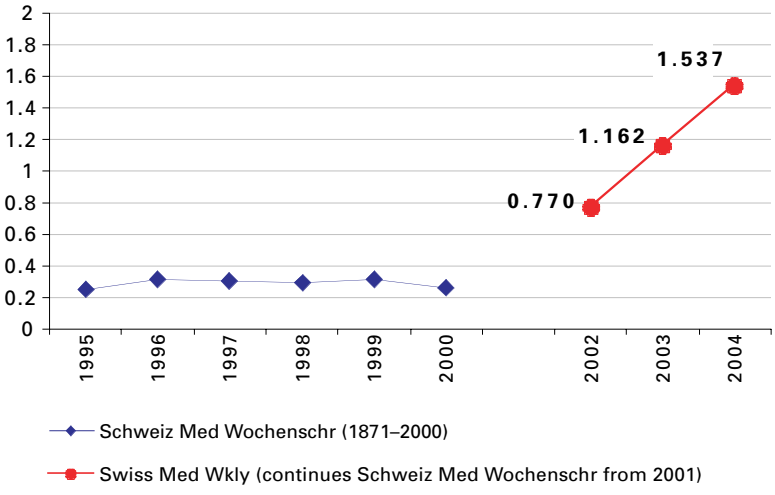

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