Drugs 1999 Jun; 57 (6): 933-940
0012-6667/99/0000-0933/$08.00/0

Salmeterol/Fluticasone Propionate Combination

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Contents

Abstract

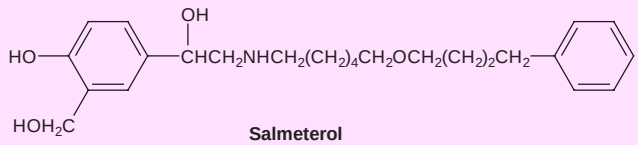
▲ Current evidence suggests that addition of the long-acting β_2-agonist salmeterol to an inhaled corticosteroid in patients with persistent asthma symptoms provides greater clinical benefit than doubling the dosage of the inhaled corticosteroid.

▲ Fixed combination salmeterol/fluticasone propionate in 3 different fluticasone propionate dosage strengths administered via the Diskus™ powder inhaler does not result in any untoward interaction that affects the pharmacodynamic or pharmacokinetic profiles of the individual drugs, or their adverse effect profiles – including the influence of the corticosteroid on plasma cortisol levels.

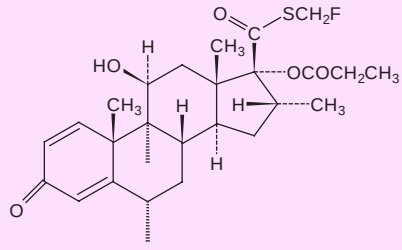
▲ Administration of fixed combination salmeterol/fluticasone propionate to both adults and children with persistent asthma provides greater improvements in lung function than either agent alone, and at least equal effectiveness to the same dosages of the 2 agents given by separate powder inhalers. Preliminary reports indicate that combination therapy has also demonstrated superior efficacy to budesonide (fluticasone propionate dosages were 25% those of budesonide).

▲ The most commonly encountered adverse effects in clinical trials with combined salmeterol/fluticasone propionate therapy have been oropharyngeal candidiasis, hoarseness/dysphonia, throat irritation, headache, tachycardia/palpitations, tremor and dizziness (all in ≤5% of patients).

Features and properties of salmeterol/fluticasone propionate	
Indications	
Regular treatment of persistent asthma where use of a combination of inhaled corticosteroid therapy plus a bronchodilator has been found to be appropriate	
Mechanism of action	
Antiasthmatic	Combination of a long-acting inhaled β_2-agonist bronchodilator and an inhaled corticosteroid
Dosage and administration	
Available dosages (salmeterol/fluticasone propionate; μg)	50/100, 50/250 or 50/500
Usual dosage	Depends on age and severity of symptoms
Route of administration	Inhalation (via Diskus™ multidose powder inhaler)
Frequency of administration	Twice daily
Pharmacokinetic profile	
Peak plasma concentration	Salmeterol 50μg: 150 ng/L fluticasone propionate ≤250μg: not detectable
Adverse events	
Most frequent	Oropharyngeal candidiasis, hoarseness/dysphonia, throat irritation, headaches, tachycardia/palpitations, tremors, dizziness and cough/breathing difficulties
Serious events	Potential adrenal suppression, as with all inhaled corticosteroids



Salmeterol



Fluticasone propionate

Salmeterol/fluticasone propionate

Fixed combinations of the long-acting β_2-agonist bronchodilator salmeterol and the corticosteroid fluticasone propionate have recently become available in 3 different fluticasone propionate dosage strengths of 50/100μg, 50/250μg and 50/500μg per inhalation, each delivered via the Diskus™ (or Accuhaler™) powder inhaler. The rationale for using these agents in combination is based on evidence that long-acting β_2-agonists and corticosteroids have complementary effects in the management of asthma. In studies in which salmeterol has been added to an inhaled corticosteroid regimen in patients inadequately controlled by the corticosteroid alone, greater improvements in symptoms and exacerbations of asthma occurred in patients receiving the combination in comparison with those who had their inhaled corticosteroid dosage doubled.[1-4] The use of such a combination is in accordance with current guidelines for the management of asthma which recommend the addition of a long-acting β_2-agonist in patients with persistent asthma in whom low to medium dosages of inhaled corticosteroids (≤500μg beclomethasone dipropionate or equivalent) plus occasional as-needed use of short-acting β_2-agonist bronchodilators do not provide satisfactory control of symptoms.[5,6]

This review will focus on studies of the fixed combination of salmeterol and fluticasone propionate given by the Diskus™ multidose powder inhaler, which has been found in previous studies to be well accepted by both adult and paediatric patients with asthma, and to be comparable in this respect to the Turbuhaler™ powder inhaler.[7,8]

1. Pharmacodynamic Properties

The pharmacodynamic properties of both salmeterol and fluticasone propionate have previously been reviewed in *Drugs*,[9-12] and readers are referred to these evaluations for more detailed accounts of the 2 agents.

- Both salmeterol and fluticasone propionate have high lipophilicity and long durations of effect at their sites of action in the lung.[13,14] The bronchodilator effect of salmeterol lasts for about 12 hours as a result of high affinity binding to an exosite located within the β_2-adrenoceptor.[9,13,15,16] Likewise, fluticasone propionate has a high affinity for the glucocorticoid receptor, and the half-life of the steroid-receptor complex is >10 hours.[14]

- Salmeterol and fluticasone propionate target different aspects of the disease process and available evidence suggest that they produce complementary

effects in patients with asthma. Although the precise mechanism(s) by which they interact to produce beneficial effects on airway function have yet to be fully elucidated, relief of residual bronchoconstriction during corticosteroid therapy, inhibition by salmeterol of endothelial cell contraction and resultant extravasation of plasma proteins, and/or a protective effect of the corticosteroid against possible β-adrenoceptor downregulation may be involved.[13,17-19]

• Salmeterol protects against histamine-, methacholine-, cold air- and sulphur dioxide-induced bronchoconstriction and exercise-induced asthma. Although there is no evidence of tolerance to the bronchodilator effects of salmeterol, some studies have shown tachyphylaxis to the bronchoprotective effects of the drug, the clinical relevance of which is unclear. Salmeterol may also have some anti-inflammatory properties and can attenuate bronchial hyper-responsiveness in patients with asthma.[9]

• Fluticasone propionate inhibits eosinophil activation and the subsequent release of inflammatory mediators. It also appears to reduce bronchial hyper-responsiveness in patients with asthma. However, as with all corticosteroids, fluticasone propionate has the potential to suppress adrenal function and cause growth impairment.[10]

• When given in fixed combination, the systemic pharmacodynamic effects of both salmeterol and fluticasone propionate are essentially unchanged in comparison with their effects when given alone or concurrently.[20] No evidence of any untoward interaction between salmeterol and fluticasone propionate was observed in single and multiple dose studies of the effects of fluticasone propionate on 24-hour urinary cortisol excretion, which was not increased by any of the 3 strengths of the combination preparation (50/100μg, 50/250μg or 50/500μg) in comparison with equivalent doses of fluticasone propionate alone. When the 50/100μg formulation was compared with placebo, no significant effect on 24-hour urinary cortisol excretion was detected.[20]

• Similarly, in a cumulative dose study comparing a total of 8 doses of the 50/500μg combination with equivalent doses of salmeterol alone, most pharmacodynamic responses to salmeterol (e.g. increased heart rate, ECG changes, decreased plasma potassium levels and increased blood glucose levels) were unaffected by the presence of fluticasone propionate, although the slope of the response curve for finger tremor per 100μg dose of salmeterol was greater with the combination preparation than with salmeterol alone. However, the final values for tremor were the same in the 2 groups.[21]

2. Pharmacokinetic Properties

Because they act locally and plasma concentrations of both salmeterol and fluticasone propionate administered by inhalation are low or undetectable, only limited pharmacokinetic information is available. Readers are referred to previous evaluations published in *Drugs* for reviews of the available information on the 2 drugs following systemic administration.[9,10] No pharmacokinetic data concerning fixed combination salmeterol/fluticasone propionate have been published.

• When salmeterol is inhaled, plasma concentrations of the drug cannot be detected, even at 30 minutes after administration of therapeutic doses. Nevertheless, in studies of single and multiple dose salmeterol, there was no evidence that concomitant administration of fluticasone propionate caused any alteration in the systemic availability of the drug versus monotherapy.[20]

• Similarly, the systemic availability of fluticasone propionate following inhalation is low, and studies comparing fluticasone propionate monotherapy with each formulation strength of fixed combination salmeterol and fluticasone propionate indicated no increase in the systemic availability of the latter when salmeterol was given concomitantly.[20]

• Both salmeterol and fluticasone propionate are metabolised by the cytochrome P450 enzyme CYP3A4, extensively so in the case of fluticasone propionate, but only partly so in the case of sal-

meterol. In this respect, no evidence of any pharmacokinetic interaction between the 2 drugs has been demonstrated when they were administered together.[20]

3. Therapeutic Use

All studies reviewed in this section refer to fixed combination salmeterol/fluticasone propionate administered by the Diskus™ powder inhaler. Most of these trials have currently been reported in abstract form only.

Adolescent and Adult Patients with Persistent Asthma

Comparisons with Salmeterol or Fluticasone Propionate Alone

- Significantly greater improvements in lung function [area under the forced expiratory volume in 1 second (FEV_1) versus time curve relative to baseline] were noted at week 12 in patients receiving twice daily combined salmeterol/fluticasone propionate therapy (50/100μg) in comparison with those receiving twice daily salmeterol (50μg) or fluticasone propionate (100μg) alone ($p \leq 0.013$). This study was randomised, double-blind, placebo-controlled and included 356 patients with mild to severe persistent asthma [baseline FEV_1 40 to 85 (mean 64)% predicted].[22-24] The onset of effect was also faster with the combination than with fluticasone propionate alone ($p < 0.001$): 85% of combination recipients achieved a ≥15% increase in FEV_1 on day 1, the median onset of effect was 28 minutes and the median duration of effect was 11 hours with this therapy (data for each agent alone were not provided).[24] Significantly fewer patients discontinued the combination due to lack of efficacy in comparison with recipients of either drug given alone or placebo (5% *vs* 24%, 12% and 44%, respectively; p values not provided).[22]

- Similarly, in a comparison of fixed combination salmeterol/fluticasone propionate (50/250μg), salmeterol (50μg) or fluticasone propionate (250μg) alone or placebo, all administered twice daily, the greatest improvements in lung function (FEV_1) within 12 hours of the first dose were obtained with the fixed combination ($p < 0.03$ *vs* all comparators). These significant differences were maintained throughout the 12-week randomised, double-blind, placebo-controlled study that was conducted in 349 patients with mild to severe persistent asthma [FEV_1 40 to 85 (mean 66)% predicted].[25,26] That the onset of action of salmeterol/fluticasone was significantly faster than that of all comparators was also shown in the number of patients with a ≥15% increase in FEV_1 within 4 hours (78, 64, 33 and 30%, respectively, $p < 0.02$ for the combination *vs* placebo and fluticasone propionate).[25] The frequency of symptoms, night awakenings, use of rescue medication and treatment withdrawal because of poor efficacy were all significantly reduced with the combination therapy versus all comparators (no p value provided).[26]

- A randomised, double-blind comparison of twice daily high-dose combined salmeterol/fluticasone propionate therapy (50/500μg) with twice daily high-dose fluticasone propionate alone (500μg) in 332 patients with persistent asthma (FEV_1 ≥50% predicted) despite ongoing treatment with corticosteroids prior to entry into the study also showed the combination to be significantly more effective in increasing both morning (the primary endpoint; fig. 1) and evening peak expiratory flow rate (PEFR) values over 12 weeks.[27,28] 171 additional patients received treatment with concurrent salmeterol and fluticasone propionate in this study (see below). Increases in symptom-free and rescue medication-free days and nights were also greater with the combination than with fluticasone propionate alone.[27]

Comparisons with Concurrent Salmeterol plus Fluticasone Propionate Administered by Separate Inhalers

- In a randomised, double-blind comparison in 244 symptomatic patients (mean baseline FEV_1 ≈75% predicted) who had been receiving inhaled corticosteroids for ≥4 weeks, fixed combination salmeterol/fluticasone propionate (50/100μg twice daily) produced slightly greater improvements in FEV_1 and mean morning (fig. 2) and evening PEFR values at 12 weeks compared with salmeterol (50μg)

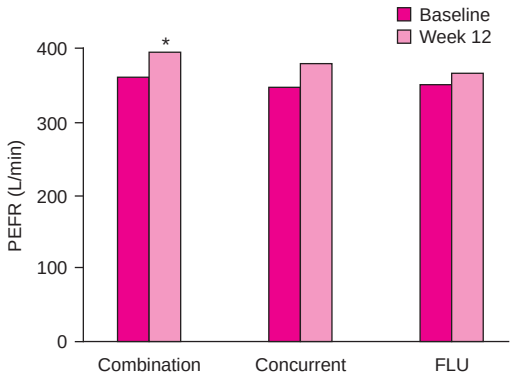


Fig. 1. Change in mean morning peak expiratory flow rate (PEFR) with fixed combination salmeterol/fluticasone propionate 50/500μg. Patients with persistent asthma (FEV_1 ≥50% predicted despite ongoing inhaled corticosteroid treatment) received 12 weeks of fixed combination salmeterol/ fluticasone propionate 50/500μg twice daily via a Diskus™ inhaler (n = 167), concurrent salmeterol 50μg twice daily plus fluticasone propionate 500μg twice daily via separate inhalers (n = 171), or fluticasone propionate 500μg twice daily alone (FLU; n = 165) in a double-blind randomised trial.[27] * $p < 0.001$ *vs* FLU.

plus fluticasone propionate (100μg) given twice daily by separate Diskus™ inhalers, but the differences between the 2 regimens were not statistically significant.[29] The mean change in mean morning PEFR from week 1 to 12 was 42 and 33 L/min for fixed combination versus concurrent therapy and values increased from 83 to 92% and 85 to 93% of predicted values, respectively. Similar improvements in the proportion of patients with no daytime symptoms or little requirement for rescue medication were observed in each treatment group.

• Similar findings were reported in 2 other randomised, double-blind trials that employed a similar design. In the first trial,[30] fixed combination salmeterol/fluticasone propionate therapy (50/250μg twice daily; n = 180) was compared with concurrent salmeterol (50μg) plus fluticasone propionate (250μg) therapy (n = 191) given twice daily by separate inhalers in symptomatic patients (mean baseline FEV_1 ≈76% predicted) who had been receiving inhaled corticosteroids for ≥4 weeks. The 2 regimens showed equivalent efficacy in improving mean morning PEFR values (43 *vs* 36 L/min improvement). Secondary endpoints including FEV_1 values, the number of symptom-free days and use of rescue medicine were also similar with each treatment. However, changes in mean evening PEFR values significantly favoured the fixed combination at all times from week 1 to 12 ($p < 0.04$). Compliance rates were equally high in the 2 treatment groups (96 and 95%, respectively).

• In the second study (some results of which are presented above), high-dose fixed combination salmeterol/fluticasone propionate (50/500μg twice daily) and concurrent salmeterol (50μg) plus high-dose fluticasone propionate (500μg) administered twice daily by separate inhalers again produced clinically equivalent responses in morning (fig. 1) and evening PEFR values over a 12-week period.[27,28] 503 patients with persistent asthma (baseline FEV_1 ≥50% predicted) despite ongoing treatment with inhaled corticosteroids were included in this trial. There were no significant differences in changes in FEV_1 values, the mean percentages of symptom-free and rescue medication-free days and nights, or in the percentage compliance rates with treatment.

Comparisons with Budesonide

• Fixed combination salmeterol/fluticasone propionate (50/100μg) twice daily produced significantly greater mean improvements in mean morning and evening PEFR than budesonide 400μg (dosage frequency not provided) in 349 patients with persistent asthma (mean baseline FEV_1 76% predicted).[31] Details of the study design were not reported. The onset of effect was faster with combination therapy than with budesonide and the benefits of combination therapy over budesonide were maintained during the 12-week study.

• In another double-blind study which enrolled 353 patients with moderate persistent asthma previously treated with inhaled corticosteroids, fixed combination salmeterol/fluticasone at the higher dosage of 50/250μg twice daily was superior to budesonide 800μg twice daily (fig. 3).[32] Recipients of the fixed combination also reported a higher frequency of symptom-free days (60 *vs* 34%; $p < 0.001$) during this 6-month trial.

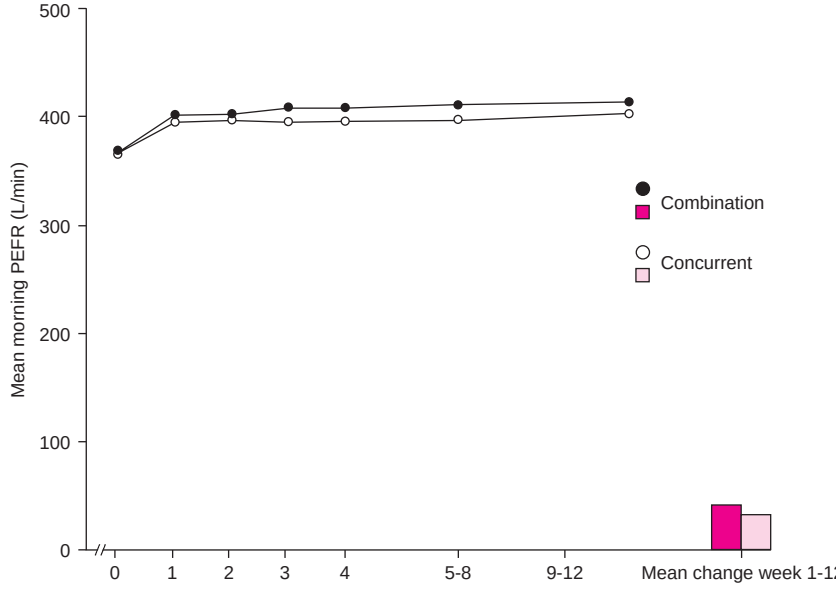


Fig. 2. Change in mean morning peak expiratory flow rate (PEFR) with fixed combination salmeterol/fluticasone propionate 50/100μg. Patients with persistent asthma (mean baseline $FEV_1 \approx 75\%$) who had been receiving inhaled corticosteroids for ≥4 weeks enrolled in a randomised, double-blind trial and received either fixed combination salmeterol/fluticasone propionate therapy 50/100μg twice daily (n = 121) or concurrent salmeterol 50μg twice daily plus fluticasone propionate 100μg twice daily given by separate Diskus™ inhalers (n = 123).[29]

Influence on Health-Related Quality of Life

• The efficacy of combined salmeterol/fluticasone propionate therapy in improving health-related quality of life (QOL), as measured by responses to the Asthma Quality of Life Questionnaire (AQLQ), was demonstrated in 2 placebo-controlled clinical trials in patients with asthma who had previously been treated with inhaled corticosteroids.[33,34]

• Combination salmeterol/fluticasone propionate 50/100μg twice daily produced significantly greater improvements in overall AQLQ score than twice daily salmeterol 50μg or fluticasone propionate 100μg alone or placebo in 356 patients with asthma (no p value reported).[34] The differences between treatments were clinically meaningful when the combination was compared with placebo or salmeterol. Sleep scores were also significantly higher with the combination in comparison with all other treatments (no p value reported).

• Analysis of responses after 12 weeks showed clinically meaningful improvements in overall QOL scores and in the 4 subscales of the AQLQ in patients receiving combination therapy at a dosage of 50/250μg twice daily in comparison with those receiving twice daily salmeterol alone (50μg) or placebo. Improvements in total AQLQ and 3 subscale scores with the combination were also significantly greater than with fluticasone propionate alone (250μg twice daily), though the differences between each regimen were only clinically meaningful for one of the subscales (emotional function).[33]

Children with Persistent Asthma

• In a randomised, double-blind trial in 257 children aged 4 to 11 years who were symptomatic despite therapy with inhaled corticosteroids, fixed combination salmeterol/fluticasone propionate (50/100μg twice daily) was as effective as concurrent salmeterol (50μg twice daily) plus fluticasone propionate (100μg twice daily) administered via separate inhalers.[35] Mean morning PEFR values improved by 33 and 28 L/min, respectively, over a period of 12 weeks. Median daytime symptom scores of zero were recorded in 61% of patients

receiving the combination and 59% receiving concurrent therapy, as compared with 14% for both groups at baseline.

4. Tolerability

The tolerability profile of the salmeterol/fluticasone propionate combination is consistent with that of its individual components (refer previous reviews in *Drugs* for a more detailed discussion of their adverse effects[9,10]).

- The incidence of adverse effects reported in the various clinical trials comparing fixed combination salmeterol/fluticasone propionate with concurrent use of the 2 drugs given by separate inhalers was similar with each treatment.[27,29,30] The most commonly encountered adverse effects with combination salmeterol/fluticasone propionate were oropharyngeal candidiasis (2 to 4% of patients), hoarseness/dysphonia (2 to 4%), throat irritation (1 to 3%), headaches (2 to 5%), tachycardia/palpitations (1 to 2%), tremors (2%), dizziness (2%) and cough/breathing difficulties (1 to 3%).[27,29,30]

- These studies also revealed no significant differences between fixed combination and concurrent salmeterol plus fluticasone propionate regimens in their effects on mean plasma cortisol concentrations or the frequency of abnormal plasma cortisol results,[27,29,30] or on 24-hour urinary cortisol excretion levels (see also section 2).[27] However, adrenal suppression can occur in occasional patients receiving fluticasone propionate, even with relatively low drug dosages (250 to 500µg per day).[36]

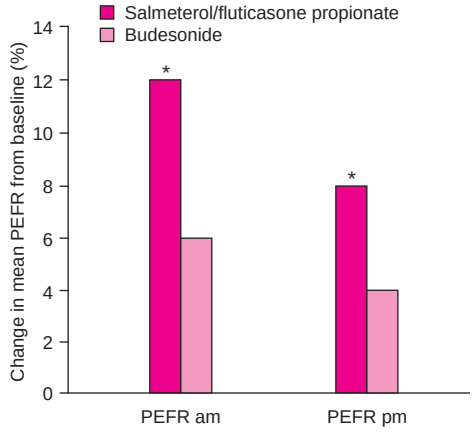


Fig. 3. Comparative efficacy of fixed combination salmeterol/fluticasone propionate (50/250µg) twice daily and budesonide 800µg twice daily in patients with moderate persistent asthma. Morning (am) and evening (pm) peak expiratory flow rate (PEFR) in 180 combination therapy recipients and 173 budesonide recipients in a double-blind 6-month trial.[32] * $p < 0.001$ *vs* budesonide.

5. Salmeterol/Fluticasone Propionate: Current Status

In clinical trials in adult patients with asthma, fixed combination salmeterol/fluticasone propionate administered via the Diskus™ multidose powder inhaler has proven more effective than monotherapy with either agent alone in improving lung function and health-related QOL. The combination, at dosages of 50/100 and 50/250µg twice daily, was also more effective than therapy with budesonide 400 and 800µg twice daily, respectively, according to preliminary reports of 2 studies.

In addition, studies in both adults and children with all 3 strengths of the combination inhaler (i.e. 50/100µg, 50/250µg and 50/500µg administered twice daily) have demonstrated similar efficacy and tolerability to concurrent therapy with the same dosages of the 2 agents given by separate inhalers.

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