

# Salmeterol and fluticasone propionate (50/250 µg) administered via combination Diskus inhaler: As effective as when given via separate Diskus inhalers

Kenneth R Chapman MD<sup>1</sup>, Nils Ringdal MD<sup>2</sup>, Vibeke Backer MD<sup>3</sup>, Mona Palmqvist MD<sup>4</sup>, Seppo Saarelainen MD<sup>5</sup>, Mark Briggs BSc<sup>6</sup>

<sup>1</sup>Toronto Hospital (Western Division), Toronto, Ontario; <sup>2</sup>Molde Hospital, Molde, Norway;

<sup>3</sup>Department of Internal Medicine, Lung Division, Bispebjerg Hospital, Copenhagen, Denmark;

<sup>4</sup>Asthma and Allergy Centre, Sahlgrenska University Hospital, Gothenberg, Sweden;

<sup>5</sup>Tampere University Hospital, Pikonlinna Hospital, Pikonlinna, Finland; <sup>6</sup>Respiratory Clinical Research, GlaxoWellcome Research and Development, Greenford, Middlesex, United Kingdom

**KR Chapman, N Ringdal, V Backer, M Palmqvist, S Saarelainen, M Briggs. Salmeterol and fluticasone propionate (50/250 µg) administered via combination Diskus inhaler: As effective as when given via separate Diskus inhalers. Can Respir J 1999;6(1):45-51.**

**OBJECTIVE:** To compare the efficacy and safety of a new combination Diskus inhaler containing both salmeterol 50 µg and fluticasone propionate 250 µg (Seretide) with the two drugs delivered via separate Diskus inhalers.

**DESIGN:** A multicentre, double-blind, double-dummy study. Three hundred and seventy-one symptomatic asthma patients (age range 13 to 75 years, mean 42 years) receiving inhaled corticosteroids were randomly assigned to two treatment groups: 28 weeks' treatment with either salmeterol/fluticasone propionate (50/250 µg bid) via a single Diskus inhaler (combination) and placebo bid via another Diskus inhaler, or salmeterol 50 µg bid via one Diskus inhaler and fluticasone propionate 250 µg bid via another (concurrent). Morning peak expiratory flow rate (PEFR) and

symptoms were measured for the first 12 weeks and safety data were collected throughout the study.

**RESULTS:** Over weeks 1 to 12, adjusted mean improvements in morning PEFR were 43 and 36 L/min for combination and concurrent therapies, respectively. The difference between the two treatment arms was 6 L/min (90% CI -13 to 0 L/min; P=0.114), which was within the predefined criteria for clinical equivalence. Adjusted mean improvements in forced expiratory volume in 1 s from baseline for week 28 were also similar between the two therapies. Thirty-five per cent of patients receiving combination inhaler and 31% of those receiving concurrent therapy had a mean daytime symptom score of zero over weeks 1 to 12 compared with 1% and 2%, respectively, at baseline. There was no difference in the incidence of adverse events between the two treatment arms. Mean serum cortisol levels were similar, and no differences in frequency of abnormal results were noted between the two groups.

**CONCLUSIONS:** This study shows that the combination of salmeterol and fluticasone propionate in a single inhaler is as ef-

*see next page*

Correspondence: Dr KR Chapman, 4-011 Edith Cavell Wing, Toronto Hospital, Western Division, 399 Bathurst Street, Toronto, Ontario M5T 2S8. Telephone 416-603-5499, fax 416-603-3456, e-mail kchapman@inforamp.net

efficacious in achieving asthma control and as well tolerated over a 28-week period as the two drugs administered individually.

**Key Words:** *Asthma, Combination therapy, Fluticasone propionate, Salmeterol*

## **Nouvel inhalateur Diskus combinant salmétérol et propionate de fluticasone (50/250 µg) : aussi efficace que deux inhalateurs Diskus utilisés séparément pour administrer chacun des médicaments**

**OBJECTIF :** Comparer l'efficacité et l'innocuité du nouvel inhalateur Diskus combinant 50 µg de salmétérol et 250 µg de propionate de fluticasone (Seretide) aux deux inhalateurs Diskus utilisés séparément pour administrer chacun des médicaments.

**MODÈLE :** Étude multicentrique, à double insu, à double placebo. Trois cent soixante et un patients asthmatiques et symptomatiques (âgés de 13 à 75 ans, moyenne de 42 ans) recevant des corticostéroïdes en inhalation ont été répartis au hasard dans deux groupes de traitement : un traitement de 28 semaines avec soit du propionate de fluticasone et du salmétérol (50/250 µg deux fois par jour) combiné dans un seul inhalateur Diskus et un placebo deux fois par jour administré au moyen d'un autre inhalateur Diskus, ou du salmétérol seul à raison de 50 µg deux fois par jour administré à l'aide d'un inhalateur Diskus et du propionate de fluticasone seul à raison de 250

µg deux fois par jour également administré par inhalateur Diskus (concomitamment). Le débit expiratoire de pointe (DEP) du matin et les symptômes ont été évalués pendant les 12 premières semaines et les données concernant l'innocuité ont été recueillies pendant toute la durée de l'étude.

**RÉSULTATS :** De la semaine 1 à la semaine 12, les améliorations moyennes corrigées du DEP du matin étaient respectivement de 43 et 36 L/min pour le traitement combiné et le traitement concomitant. La différence entre les deux branches de traitement était de 6 L/min (IC de 90 %; 13 à 0 L/min ;  $p = 0,114$ ), donc dans les limites des critères prédéfinis pour l'équivalence clinique. Les améliorations moyennes corrigées pour le volume expiratoire maximal/seconde à partir des valeurs de base pour la 28 semaine étaient aussi similaires entre les deux traitements. Trente-cinq pour cent de patients recevant la combinaison des deux médicaments avec un seul inhalateur et 31 % de ceux recevant les deux médicaments concomitamment accusaient un score moyen de symptômes diurnes de zéro de la semaine 1 à la semaine 12 comparativement à 1 % et 2 %, respectivement, aux valeurs de base. On n'a observé aucune différence dans l'incidence des effets indésirables entre les deux branches de traitement. Les taux moyens de cortisol sérique étaient similaires, et aucune différence dans la fréquence de résultats anormaux n'a été notée entre les deux groupes.

**CONCLUSIONS :** La présente étude démontre qu'une combinaison de salmétérol et de propionate de fluticasone administrée par le biais d'un seul inhalateur se révèle aussi efficace à maîtriser l'asthme et est aussi bien tolérée pendant une période de 28 semaines que les deux médicaments administrés séparément.

Asthma is a chronic disease of the lungs characterized by Airway inflammation, bronchoconstriction and increased airway responsiveness to challenge (such as allergen or spasmogen). Inhaled corticosteroids improve lung function and symptom control, decrease bronchial hyperresponsiveness and reduce the frequency of exacerbations in patients with asthma (1-5). However, the dose-response curve to inhaled corticosteroids is not linear. In patients whose asthma is incompletely controlled with a moderate daily dose of inhaled corticosteroid, greater symptom control is achieved by the addition of a long-acting beta<sub>2</sub>-agonist than by doubling the dose of inhaled corticosteroid. Two studies have demonstrated that the addition of salmeterol, a long-acting beta<sub>2</sub>-agonist, to existing inhaled beclomethasone dipropionate (BDP) therapy provides more effective control of symptoms than doubling the dose of BDP (6,7). Similar findings have been reported for the combination of salmeterol and fluticasone propionate (8,9), and for the combination of formoterol and budesonide (10).

Combining long-acting inhaled agents such as salmeterol (11,12) with potent, topically active, inhaled corticosteroids such as fluticasone propionate (13) has been recognized as a potentially useful management strategy in asthma of moderate or greater severity (14-16). Employing this combination strategy not only improves the control of symptoms better than inhaled corticosteroids alone but also allows for the use of lower doses of inhaled corticosteroid, presumably lowering any risk of systemic side effects from the inhaled corticosteroid (17-19). Although some have speculated that the long term use of long-acting beta<sub>2</sub>-agonists might be associated with increased exacerbations, the opposite appears to be true. Nonetheless, combination maintenance therapy is not

without potential problems. Most obvious, compliance is thought to suffer as the complexity of the regimen increases (20,21). The availability of a long-acting beta<sub>2</sub>-agonist and an effective inhaled corticosteroid in a single combination inhaler would diminish the risk of suboptimal compliance and, in particular, would ensure that patients using such beta<sub>2</sub>-agonists would always use the anti-inflammatory corticosteroid concurrently.

The primary objective of this study was to determine whether salmeterol and fluticasone propionate dry powder in combination (Seretide, Glaxo Wellcome, UK) via one Diskus (Glaxo Wellcome Inc) inhaler (known as the Accuhaler inhaler in some countries) show clinical equivalence compared with the two active components at equivalent dosage delivered by separate Diskus inhalers. The secondary objective of this study was to demonstrate the safety of salmeterol and fluticasone propionate in combination over a 28-week treatment period.

### **PATIENTS AND METHODS**

This multicentre, randomized, double-blind, double-dummy, parallel group study was performed in 43 centres in five countries. The study conformed to Good Clinical Practice Guidelines and to the Declaration of Helsinki 1964, as modified by the 41st World Medical Assembly, Hong Kong, 1989; local ethics committee approval was obtained at all participating sites. All patients provided written informed consent; in the case of minors, this consent was given by their parents or guardians.

During the initial two-week run-in period, patients continued to take inhaled BDP or budesonide 800 to 1200 µg/day, or fluticasone propionate 400 to 600 µg/day, and any bron-

**TABLE 1**  
Day and night-time scores definitions used in the study of salmeterol plus fluticasone propionate in one inhaler

| Score      | Definition  |
|------------|---|
| Daytime    |   |
| 0          | No symptoms during the day  |
| 1          | Symptoms for one short period during the day  |
| 2          | Symptoms for two or more short periods during the day                                 |
| 3          | Symptoms for most of the day 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 work or school and normal daily activity        |
| Night-time |   |
| 0          | No symptoms during the night  |
| 1          | Symptoms causing awakening once during the night or early awakening                   |
| 3          | 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  |

chodilator therapy was replaced by salbutamol via a Diskhaler inhaler or a pressurized metered-dose inhaler for relief of symptoms as required. During the 28-week treatment period, patients received either salmeterol and fluticasone propionate (50/250 µg bid) in combination (Seretide) via a single Diskus inhaler (combination therapy) and placebo bid via another Diskus inhaler, or the same dosages of the active components via separate Diskus inhalers (concurrent therapy). Patients also had access to salbutamol via a Diskhaler inhaler or a pressurized metered-dose inhaler for symptomatic bronchodilator use. Completion of the study or withdrawal was followed by a two-week period during which patients received their usual prescribed medications.

**Patients:** Patients aged 12 years or older with symptomatic asthma despite inhaled corticosteroids were eligible for participation in the study. Inclusion criteria included a documented clinical history of reversible airways obstruction and treatment with BDP, budesonide (both 800 to 1200 µg/day range of doses or two different doses) or fluticasone propionate (400 to 600 µg/day) for at least four weeks before starting treatment. All eligible patients had a symptom score (day-time plus night-time) totalling at least two on at least four of the last seven consecutive days during the run-in period. Day- and night-time scores are defined in Table 1. An additional inclusion criterion (to insure that there was the potential for responsiveness to the active comparators) was a mean morning peak expiratory flow rate (PEFR) (calculated from the last seven days of the run-in period) of 50% to 85% of PEFR measured 15 mins after administration of salbutamol 400 µg at the start of treatment.

**TABLE 2**  
Patient demographics and characteristics at baseline

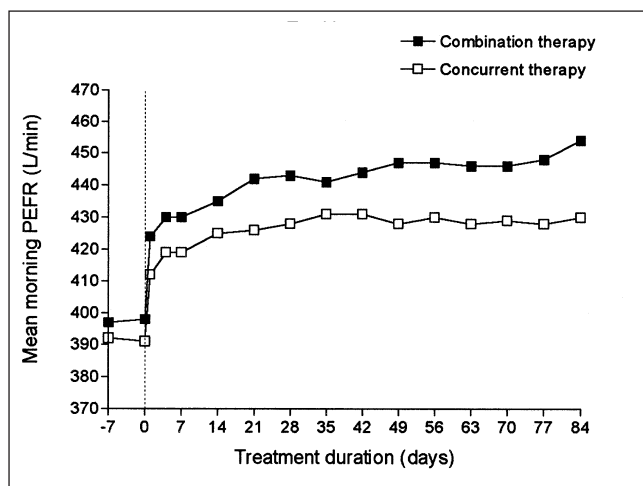
| Characteristics                                    | Treatment group   |  |
|--|---|--|
|  | Salmeterol/<br>fluticasone<br>propionate<br>(combination;<br>50/250 µg bid) | Salmeterol<br>(50 µg bid) plus<br>fluticasone<br>propionate<br>(concurrent;<br>250 µg bid) |
| Number of patients                                 | 180   | 191  |
| Sex, n (%)   |   |  |
| Female   | 88 (49)   | 109 (57)   |
| Male   | 92 (51)   | 82 (43)  |
| Mean age, years (range)                            | 42.8 (13-73)  | 41.4 (15-75)   |
| Smoking history, n (%)                             |   |  |
| Current  | 27 (15)   | 25 (13)  |
| Ex-smoker  | 53 (29)   | 69 (36)  |
| Never  | 100 (56)  | 97 (51)  |
| Mean baseline PEFR, L/min (% predicted), n (%)     |   |  |
| Morning  | 398 (84)  | 391 (85)   |
| Evening  | 415 (88)  | 415 (89)   |
| Mean baseline FEV <sub>1</sub> (L) (% predicted)   | 2.51 (75)   | 2.55 (77)  |
| Patients using concurrent asthma medication, n (%) |   |  |
| Methylxanthines                                    | 7 (4)   | 6 (3)  |
| Ipratropium bromide                                | 2 (1)   | 1 (<1)   |

FEV<sub>1</sub> Forced expiratory volume in 1 s; PEFR Peak expiratory flow rate

Exclusion criteria included treatment with salmeterol or any other long-acting inhaled beta<sub>2</sub>-agonist in the four weeks before recruitment; lower respiratory tract infection or treatment with corticosteroids (oral, depot or parenteral) within four weeks of the run-in period; treatment with two or more courses of oral, depot or parenteral corticosteroids within 12 weeks of the run-in period; acute exacerbation of reversible airways obstruction that required hospitalization within 12 weeks of the run-in period; or a smoking history of 10 pack-years or greater (ie, 10 cigarettes/day for 20 years or 20 cigarettes/day for 10 years or 40 cigarettes/day for five years).

Patients were assessed at the beginning of the run-in and treatment periods, at two, four, eight, 12, 20 and 28 weeks after randomization and again two weeks after cessation of double-blind treatment. At each of these visits, forced expiratory volume in 1 s (FEV<sub>1</sub>) was recorded as the highest value of at least three maximal and reproducible efforts. Physical examination included blood pressure and heart rate recordings as well as inspection of the oropharynx for evidence of candidiasis. At the beginning of treatment and at 12 and 28 weeks, a fasting blood sample was taken for determination of laboratory parameters including serum cortisol levels.

Efficacy measurements were recorded for the first 12 weeks of the study only. The primary efficacy variable was mean morning PEFR. Throughout the study, patients measured their morning and evening PEFR using a mini-Wright peak flow meter (Clement Clarke Inc, Ohio); three measurements were made on each occasion, and the highest value was recorded in a daily record card. All PEFR measurements were made before inhalation of study medication or rescue



**Figure 1** Mean morning peak expiratory flow rate (PEFR) values in asthma patients at baseline and during 12 weeks' treatment with either salmeterol/fluticasone propionate 50/250 µg bid (combination therapy) or salmeterol 50 µg bid plus fluticasone propionate 250 µg bid (concurrent therapy)

salbutamol. Patients recorded their use of rescue salbutamol, together with their daytime and night-time symptom score in the daily record card.

Compliance of patients with treatment was calculated (as a percentage) as the number of doses used (assessed on the dose counter on the inhalers) divided by the expected use.

**Statistical analysis:** All analyses were performed on an intention-to-treat basis. Mean PEFR and FEV<sub>1</sub> values were analyzed using analysis of covariance, and symptom score and use of rescue medication were analysed using the Wilcoxon rank sum test. The proportion of withdrawals in each treatment group was compared using the  $\chi^2$  test. Treatment equivalence was tested using the 90% CI of the difference between the combination and concurrent therapies in mean morning PEFR. (Although the 90% CI was used to assess bioequivalence, the 95% CI was also determined). A priori equivalence was regarded as a 90% CI within  $\pm 15$  L/min, a value used in previous clinical studies (22) and considered to represent a difference of potential clinical relevance.

## RESULTS

The demographic and disease characteristics of 371 randomized patients are given in Table 2 and were similar for the two treatment groups. After randomization, 36 patients were withdrawn, comprising 20 (11%) from the combination therapy group and 16 (8%) from the concurrent therapy group. There was no significant difference in the number of withdrawals from each treatment group. The most common reason for withdrawal was adverse events (see below); other reasons included failure to return for follow-up (n=6), non-compliance (n=2) and not fulfilling the entry criteria (n=2).

Mean compliance (mean of medication used expressed as a percentage of expected use) during weeks 1 to 12 was 96% and 95% in the combination and concurrent therapy groups, respectively, and during weeks 1 to 28 was 95% and 94%, respectively.

### Mean morning PEFR and percentage predicted mean morning PEFR:

For both treatments, mean morning PEFR improved significantly throughout the first 12 weeks of treatment compared with baseline. Mean adjusted changes from baseline were 43 and 36 L/min for combination and concurrent therapy, respectively (Figure 1). Over the first 12 weeks of treatment, the difference between the two treatment arms (concurrent-combination) for the increase in mean morning PEFR was -6 L/min, with the 90% CI (-13 to 0 L/min) being within the equivalence definition of 15 L/min. The 95% CI (-14 to 2 L/min) was also within the equivalence definition. While the difference between the two treatments for adjusted change in mean morning PEFR at some time points was similar to that reported for weeks 1 to 12, confidence limits were outside the equivalence definition and there was a statistically significant difference at weeks 3 and 4 (90% CI -16 to -2 L/min, P=0.037; and 90% CI -16 to -2 L/min, P=0.043, respectively).

The mean morning PEFR baseline values were 84% and 85% of predicted for the combination and concurrent therapies, respectively, and both treatment arms improved this measure of lung function throughout the treatment period: the adjusted mean changes in predicted morning PEFR compared with baseline for weeks 1 to 12 were 9% and 7% for the combination and concurrent therapies, respectively. The

**TABLE 3**

**Changes in mean evening peak expiratory flow rate (PEFR) and percentage predicted mean evening PEFR during 12 weeks' treatment with either salmeterol 50 µg bid plus fluticasone propionate 250 µg bid (concurrent therapy [Conc]) or salmeterol/fluticasone propionate, 50/250 µg bid (combination therapy [Comb]) in patients with asthma**

| Time          | Change in mean evening PEFR (L/min) |      |                     |       | Change in % predicted mean evening PEFR |      |                     |        |
|---------------|-------------------------------------|------|---------------------|-------|---|------|---------------------|--------|
|               | Conc                                | Comb | Difference (90% CI) | P     | Conc                                    | Comb | Difference (90% CI) | P      |
| Week 1        | 21                                  | 28   | -7 (-13 to -1)      | 0.039 | 4                                       | 6    | -2 (-3 to 0)        | 0.026  |
| Week 2        | 22                                  | 32   | -10 (-16 to -3)     | 0.012 | 4                                       | 7    | -2 (-4 to -1)       | 0.006  |
| Week 3        | 24                                  | 37   | -13 (-19 to -6)     | 0.001 | 5                                       | 8    | -3 (-4 to -2)       | <0.001 |
| Week 4        | 25                                  | 36   | -11 (-18 to -4)     | 0.006 | 5                                       | 8    | -3 (-4 to -1)       | 0.002  |
| Weeks 5 to 8  | 24                                  | 36   | -11 (-18 to -4)     | 0.008 | 5                                       | 8    | -3 (-4 to -1)       | 0.003  |
| Weeks 9 to 12 | 26                                  | 36   | -10 (-17 to -3)     | 0.020 | 5                                       | 8    | -2 (-4 to -1)       | 0.009  |
| Weeks 1 to 12 | 25                                  | 35   | -10 (-16 to -4)     | 0.008 | 5                                       | 7    | -2 (-4 to -1)       | 0.002  |

weeks 1 to 12 treatment difference was  $-2\%$  (90% CI  $-3$  to  $0\%$ ;  $P=0.052$ ).

**Mean evening PEFR and percentage predicted mean evening PEFR:** In both treatment arms, mean evening PEFR during the first 12 weeks' treatment was improved significantly compared with baseline. Adjusted mean changes in evening PEFR were 35 and 25 L/min for combination and concurrent therapy, respectively (Table 2). During weeks 1 to 12, the mean difference between the two treatments for this parameter was  $-10$  L/min (90% CI  $-16$  to  $-4$  L/min;  $P=0.008$ ). Statistically significant differences in mean evening PEFR favoured the combination product at all time points (Table 3). Parallel findings were seen when evening PEFR was expressed as a percentage of the predicted normal value (Table 3).

**FEV<sub>1</sub>:** Both combination and concurrent therapy improved FEV<sub>1</sub> at each clinic visit during the 28-week treatment period compared with baseline; adjusted mean changes at week 28 were 0.26 and 0.24 L/min, respectively. At week 28, the treatment difference was  $-0.02$  L/min (90% CI  $-0.09$  to  $0.05$  L/min).

**Symptom scores and percentage of symptom-free days or nights:** At baseline, 1% of patients ( $n=1$ ) treated with combination therapy and 2% ( $n=4$ ) receiving concurrent therapy had a median daytime symptom score of zero; after 12 weeks' treatment, this increased to 35% ( $n=63$ ) and 32% ( $n=61$ ) in these two groups, respectively. Thirty-four per cent ( $n=61$ ) of patients treated with combination therapy and 30% ( $n=58$ ) receiving concurrent therapy had a median night-time symptom score of zero at baseline; this increased to 62% ( $n=111$ ) and 53% ( $n=101$ ) of patients, respectively, during weeks 1 to 12. For both median daytime and night-time symptom scores, there were no significant differences between the treatment groups.

The percentage of patients with 75% or more symptom-free days increased from 1% ( $n=1$ ) at baseline to 22% ( $n=39$ ) during treatment for those receiving combination therapy, and from 1% ( $n=1$ ) to 15% ( $n=29$ ) for those receiving concurrent therapy. The median difference between concurrent minus combination therapy was 0% (90% CI  $-4$  to  $0\%$ ).

The percentage of patients with 75% or more symptom-free nights increased from 23% ( $n=41$ ) at baseline to 48% ( $n=86$ ) during combination therapy, and from 20% (39) to 42% ( $n=80$ ) for patients receiving concurrent therapy. The median difference between treatments was  $-3\%$  (90% CI  $-9$  to  $0\%$ ).

**Use of salbutamol as needed:** At baseline, 6% of patients ( $n=10$ ) treated with combination therapy and 11% ( $n=21$ ) treated with concurrent therapy did not require salbutamol on 75% or more of days. During the first 12 weeks of treatment, this increased to 40% ( $n=72$ ) and 34% ( $n=64$ ), respectively. The median treatment difference of concurrent minus combination therapy ( $-4\%$ ) was not statistically significant (90% CI  $-11$  to  $0\%$ ). Similar results were found for analyses of other time periods within the study. At baseline, 47% of patients ( $n=85$ ) in each treatment group did not require salbutamol on 75% or more of nights. During the treatment period, 69% ( $n=125$ ) and 62% ( $n=118$ ) of patients treated with com-

**TABLE 4**  
Summary of the most commonly reported (2% or more in either treatment group) drug-related adverse events during treatment with either salmeterol/fluticasone propionate 50/250  $\mu\text{g}$  bid (combination) or salmeterol 50  $\mu\text{g}$  bid plus fluticasone propionate 250  $\mu\text{g}$  bid (concurrent) over a 28-week period

| Adverse event                     | Treatment group |            |
|-----------------------------------|-----------------|------------|
|                                   | Combination     | Concurrent |
| Headaches                         | 9 (5%)          | 10 (5%)    |
| Candidiasis                       |                 |            |
| Mouth/throat                      | 8 (4%)          | 7 (4%)     |
| Nonspecific site                  | 3 (2%)          | 1 (<1%)    |
| Hoarseness or dysphonia           | 7 (4%)          | 7 (4%)     |
| Throat irritation                 | 5 (3%)          | 5 (3%)     |
| Upper respiratory tract infection | 4 (2%)          | 3 (2%)     |
| Asthma                            | 4 (2%)          | 3 (2%)     |
| Palpitations                      | 4 (2%)          | 2 (1%)     |
| Tremors                           | 4 (2%)          | 1 (<1%)    |
| Dizziness                         | 3 (2%)          | 1 (<1%)    |
| Chest symptoms                    | 3 (2%)          | 0          |

bination and concurrent therapy, respectively, did not require rescue salbutamol. The median treatment difference was  $-3\%$  (90% CI  $-6$  to  $0\%$ ).

**Safety:** All patients enrolled ( $n=371$ ) were included in the safety analysis. Overall, both treatment regimens were well tolerated throughout the 28-week study. A total of 324 patients (160 combination and 164 concurrent therapy) reported an adverse event during treatment. Drug-related adverse events that occurred with a frequency of 2% or more in either treatment group are listed in Table 4. A total of 21 patients withdrew from therapy because of an adverse event (12 patients treated with combination therapy and nine with concurrent therapy). Ten of these events (five in each group) were asthma-related. Overall, there were no differences between the two treatments in terms of adverse events resulting in treatment withdrawal.

No clinically significant changes in laboratory values, physical examinations or vital signs were observed in either treatment group. Mean serum cortisol concentrations were not significantly different between treatments before or during therapy.

## DISCUSSION

Our findings confirm the benefit of adding salmeterol to inhaled corticosteroid when asthma is suboptimally controlled by inhaled corticosteroid alone. Patients in both active treatment groups showed marked improvements in pulmonary function and symptom control compared with their baseline when asthma control was sought with moderate doses of inhaled corticosteroid alone. More important, our study found that salmeterol 50  $\mu\text{g}$  twice daily and fluticasone propionate 250  $\mu\text{g}$  twice daily was as effective when given via a single combination Diskus inhaler as when given sepa-

rately via two Diskus inhalers. This therapeutic equivalence was not the consequence of patients in both treatment groups reaching the plateau of their dose-response curves. We regarded the postsalbutamol peak flow rate at the randomization visit to be the patient's personal best peak flow. During the run-in period, the mean morning PEFr was 79% of this response in both treatment groups. During active treatment, this value increased but the mean percentage in both groups did not exceed 89% of the patient's personal best value. That is, there remained some room for detecting possible differences in efficacy between treatment formulations. Of course, a mean active treatment PEFr for the group equal to 89% of each patient's personal best value suggests that a subset of patients did reach this personal best value. The larger this subset is, the larger would be the plateau effect limiting our ability to detect therapeutic inequivalence between groups.

One unanticipated finding of our study was that some morning PEFr values and some evening PEFr values were higher in patients treated with the combination Diskus inhaler than in patients treated with the separate Diskus inhalers. Such a finding would not have been surprising in an open (nonblind) study. That is, the anticipated greater compliance with a single inhaler formulation than with two maintenance inhalers might account for greater clinical effectiveness. But our study was of a double-blind design, and both treatment groups self-administered from two Diskus inhalers twice daily. It is possible that some of the patients experimented with their study medications and became nonblinded to study medication. One would then postulate greater compliance in patients randomly assigned to receive the combination regimen. This explanation seems unlikely, however, because compliance (as measured by the Diskus dose counter) was equivalent and was quite high in both active treatment groups. Only surreptitious 'dose-dumping' would make this explanation feasible. In a somewhat different but related fashion, a difference in compliance could explain the sometimes greater benefit of the combination inhaler. In cases where patients omitted one of the study inhalers, patients who had inadvertently omitted the active combination inhaler would perhaps more rapidly perceive the consequences of their noncompliance.

Our study did not directly compare the compliance of patients using separately administered drugs with the compliance of patients using drugs administered via combination inhaler. However, it seems likely that the decreased complexity of the latter regimen would lead to greater compliance in the clinical setting (20,21). There might also be cost savings, in that pharmacy dispensing fees would be lower for single combination inhalers than for separate inhalers containing equivalent doses of medication. There are relatively few disadvantages to the combination approach, but these should also be considered. One disadvantage is an inability to administer either maintenance agent in once daily fashion. For most patients, once daily inhaled corticosteroid does not seem to produce optimal disease control. However, once daily salmeterol is a plausible strategy for patients seeking to limit either frequent daytime symptoms or frequent night-

time symptoms requiring only morning or evening self-administration, respectively.

Some limits of our study should be noted. First, we assessed only one combination regimen of salmeterol plus fluticasone propionate. It would be desirable in the clinical setting to have some dosing flexibility and the option to administer various dosage combinations of these two agents. In particular, it would be desirable to have several dosages of fluticasone propionate combined with salmeterol so as to allow for titration of the inhaled corticosteroid moiety of the regimen to the lowest possible dose consistent with adequate disease control. Such alternative formulations are under development and are being tested in separate clinical trials. Second, our study did not assess exacerbations as a treatment outcome. Our study was not designed to address this outcome in that there was no control group not receiving salmeterol and the study was relatively short for a meaningful number of exacerbations to occur. Third, our study found no evidence of tolerance to the 28-week administration of salmeterol. However, the study was not designed to address this issue, but its findings are consistent with the suggestion that any degree of tolerance is modest and of minimal clinical impact.

## CONCLUSIONS

Our findings reassure that the combination of salmeterol 50 µg twice daily and fluticasone 250 µg twice daily administered via a single Diskus inhaler is as effective and safe as the same dosage of these drugs given via separate inhalers. Additional studies determining the effectiveness of other dosage combinations of these agents in the maintenance and control of asthma are being published (23). Additional open (nonblind) studies will be helpful in assessing compliance and the clinical impact of such a combination formulation compared with separate formulations of these maintenance drugs.

---

**ACKNOWLEDGEMENTS:** This study was sponsored by Glaxo Wellcome Research and Development (SFCB3018).

---

## REFERENCES

1. Chervinsky P, van-As A, Bronsky EA, et al. Fluticasone propionate aerosol for the treatment of adults with mild to moderate asthma. The Fluticasone Propionate Asthma Study Group. *J Allergy Clin Immunol* 1994;94:676-83.
2. Fabbri L, Burge PS, Croonenborgh L, et al. Comparison of fluticasone propionate with beclomethasone dipropionate in moderate to severe asthma treated for one year. International Study Group. *Thorax* 1993;48:817-23.
3. Noonan M, Chervinsky P, Busse WW, et al. Fluticasone propionate reduces oral prednisone use while it improves asthma control and quality of life. *Am J Respir Crit Care Med* 1995;152:1467-73.
4. Haahtela T, Järvinen M, Kava T, et al. Comparison of a beta<sub>2</sub>-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med* 1991;325:388-92.
5. Juniper EF, Kline PA, Vanzielegheem MA, Hargreave FE. Reduction of budesonide after a year of increased use: a randomized controlled trial to evaluate whether improvements in airway responsiveness and clinical asthma are maintained. *J Allergy Clin Immunol* 1991;87:483-9.
6. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. *Lancet* 1994;344:219-24.

7. Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. *Am J Respir Crit Care Med* 1996;153:1481-8.
  8. Ind PW, Dal Negro R, Colman NC, et al. Inhaled fluticasone propionate and salmeterol in moderate adult asthma. I: Lung function and symptoms. *Am J Respir Crit Care Med* 1998;157:A416. (Abst)
  9. Ind PW, Dal Negro R, Colman NC, et al. Inhaled fluticasone propionate and salmeterol in moderate adult asthma II: Exacerbations. *Am J Respir Crit Care Med* 1998;157:A415. (Abst)
  10. Pauwels RA, Löfdahl CG, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med* 1997;337:1405-11.
  11. Blom MW, De Sommers K. Comparative pharmacology of salmeterol and formoterol and their interaction with salbutamol in healthy volunteers. *Clin Drug Invest* 1997;14:400-4.
  12. Brogden RN, Faulds D. Salmeterol xinafoate. A review of its pharmacological properties and therapeutic potential in reversible obstructive airways disease. *Drugs* 1991;42:895-912.
  13. Holliday SM, Faulds D, Sorkin EM. Inhaled fluticasone propionate. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in asthma. *Drugs* 1994;47:318-31.
  14. British Thoracic Society. The British Guidelines on Asthma Management. *Thorax* 1997;52(Suppl 1):S1-21.
  15. Global strategy for asthma management and prevention. World Health Organization/National Institutes of Health, National Heart, Lung, and Blood Institute (NHLBI) Workshop Report [publication number 95-3659]. Bethesda: NHLBI, 1995.
  16. Ernst P, Fitzgerald JM, Spier S. Canadian asthma consensus conference: Summary of recommendations. *Can Respir J* 1996;3:89-100.
  17. Hanania NA, Chapman KR, Sturtridge WC, Szalai JP, Kesten S. Dose-related decrease in bone density among asthmatic patients treated with inhaled corticosteroids. *J Allergy Clin Immunol* 1995;96:571-9.
  18. Hanania NA, Chapman KR, Kesten S. Adverse effects of inhaled corticosteroids. *Am J Med* 1995;98:196-208.
  19. Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. *N Engl J Med* 1997;337:8-14.
  20. Eisen SA, Miller DK, Woodward RS, et al. The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med* 1990;150:1881-4.
  21. Coutts JAP, Gibson NA, Paton JY. Measuring compliance with inhaled medication in asthma. *Arch Dis Child* 1992;67:332-3.
  22. Boulet LP, Cowie R, Johnston P, et al. Comparison of Diskus inhaler, a new multidose powder inhaler, with Diskhaler inhaler for the delivery of salmeterol to asthmatic patients. Canadian Study Group. *J Asthma* 1995;32:429-36.
  23. Bateman ED, Britton M, Carrillo T, Almeida J, Wixon C. Salmeterol/fluticasone (50/100mcg) combination inhaler. A new, effective and well tolerated treatment for asthma. *Clin Drug Invest* 1998;16:193-201.
-



**Hindawi**  
Submit your manuscripts at  
<http://www.hindawi.com>

