Clin Drug Invest 1998 Sep; 16 (3): 193-201
1173-2563/98/0009-0193/$04.50/0



# Salmeterol/Fluticasone Combination Inhaler

## A New, Effective and Well Tolerated Treatment for Asthma

*E.D. Bateman*,[1] *M. Britton*,[2] *J. Carrillo*,[3] *J. Almeida*[4] and *C. Wixon*[5]

1 University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa
2 St Peters Hospital, Chertsey, Surrey, England
3 Seccion de Algergia, Hospital Universtario, Las Palmas, de Gran Canaria, Spain
4 Hospital de Sao Joao, Servico de Pneumalogia, Porto, Portugal
5 Respiratory Clinical Research, GlaxoWellcome Research and Development, Greenford, Middlesex, England

## Abstract

**Objective:** The efficacy and tolerability of a new combination inhaler containing both salmeterol 50µg and fluticasone 100µg in a single device was compared with the delivery of the two drugs via two separate inhalers in a multicentre, double-blind, double-dummy study.

**Patients:** 244 symptomatic asthma patients (age range 12 to 78 years) were randomised to a 12-week treatment period with either salmeterol/fluticasone (50/100µg twice daily) via a single inhaler (combination) and placebo twice daily via another, or salmeterol 50µg twice daily via one inhaler and fluticasone 100µg twice daily via another (concurrent).

**Results:** Morning peak expiratory flow rate (PEFR), symptoms and tolerability were collected throughout the treatment period. Adjusted mean improvements in morning PEFR were 42 and 33 L/min for combination and concurrent therapies, respectively, over the 12-week treatment period. Adjusted mean improvements in forced expiratory volume in 1 second ($FEV_1$) from baseline at week 12 were 0.20 and 0.17L for combination and concurrent therapies, respectively. 60% of patients receiving combination inhaler and 64% of those receiving concurrent therapy had a mean daytime symptom score of zero over the treatment period compared with 17 and 15%, respectively, at baseline. Both treatments were well tolerated. Geometric mean morning serum cortisol levels were similar and no differences in the frequency of abnormal results were noted between the two groups.

**Conclusion:** This was the first study reporting the control of asthma by administration of salmeterol and fluticasone in combination via a single inhaler. The new combination inhaler was as effective and well tolerated as the two drugs administered individually and has potential advantages in terms of convenience.

National and international asthma treatment guidelines recommend the early introduction of inhaled corticosteroids in persistent asthma.[1,2] This is supported by the recognition of chronic inflammation as the underlying pathological basis of asthma (at all levels of severity). Inhaled corticosteroids have been shown to improve lung function and symptom control, to decrease bronchial hyperresponsiveness, and to reduce the rate of asthma exacerbations.[3-7]

Two separate studies have demonstrated the addition of the long-acting $\beta_2$-agonist, salmeterol, to existing inhaled corticosteroid therapy, beclomethasone, to be more effective for asthma control than doubling the dose of the inhaled corticosteroid.[8,9] A more recent study has reported significantly improved lung function[10] and a significantly decreased number of severe exacerbations[11] in those patients receiving salmeterol in combination with fluticasone compared with those receiving double the dose of inhaled corticosteroid. A greater reduction in the rate of exacerbation in patients with asthma receiving the combination of a long-acting $\beta_2$-agonist and an inhaled corticosteroid compared with inhaled corticosteroid alone has been reported.[12]

Guidelines now recommend the option of introducing a long-acting $\beta_2$-agonist to patients who remain symptomatic on either beclomethasone or budesonide 100 to 400μg twice daily or fluticasone 50 to 200μg twice daily instead of increasing the dose of inhaled corticosteroid.[1]

In view of the increasing evidence of a benefit of combining salmeterol use with that of inhaled corticosteroids, a set of inhalers containing a combination of salmeterol and fluticasone in commonly used ratios of salmeterol to fluticasone have been developed.

The objective of this study was to determine whether salmeterol/fluticasone in a 50/100μg ratio of salmeterol to fluticasone, administered twice daily in combination (Seretide®) via one Diskus® inhaler (known as the Accuhaler® inhaler in some countries) showed clinical equivalence and comparable tolerability compared with the two active components, salmeterol 50μg twice daily via one Diskus® inhaler and fluticasone 100μg twice daily via a second Diskus® inhaler, in patients who were symptomatic on their previous dose of inhaled corticosteroid therapy, over a 12-week treatment period.

## Patients and Methods

### Study Design

This study was a multicentre, randomised, double-blind, double-dummy, parallel-group study performed in 44 centres in four 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; ethics committee approval was also obtained.

All patients had given written informed consent (in the case of a minor this was given by their parent/guardian). During the initial 2-week run-in period patients continued to take their inhaled corticosteroid therapy and any bronchodilator therapy was replaced by salbutamol via a Diskhaler® inhaler or a pressurised metered-dose inhaler for relief of symptoms as required.

During the 12-week treatment period, patients received either salmeterol/fluticasone (50/100μg twice daily) in combination (Seretide®) via one Diskus® inhaler (combination therapy) and placebo twice daily via another Diskus® inhaler, or salmeterol 50μg twice daily via one Diskus® inhaler and fluticasone 100μg twice daily via another Diskus® inhaler (concurrent therapy). Patients were also provided with salbutamol in the form of a Diskhaler® inhaler or a pressurised metered-dose inhaler for symptomatic use. Completion of the study or withdrawal from it was ensued by a 2-week follow-up period during which patients received their normal prescribed medication.

### Study Participants

Patients aged ≥12 years with symptomatic asthma who completed the run-in period were ran-

domly assigned to study treatment. Treatment numbers obtained from a computer-generated randomisation code were assigned in blocks of four to each centre. The latter allocated the lowest available number in consecutive order. Inclusion criteria involved having a documented clinical history of reversible airways obstruction, and receiving beclomethasone or budesonide 400 to 500 μg/day or fluticasone 200 to 250 μg/day for ≥4 weeks prior to the start of treatment.

For inclusion into the treatment period patients had to have recorded a symptom score (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 which did not affect normal daily activity; 4 = symptoms for most of the day which did affect normal daily activity; 5 = symptoms so severe that they affected work/school and normal daily activity; night-time: 0 = no symptoms during the night; 1 = symptoms causing awakening once during the night or early awakening; 2 = symptoms causing awakening twice or more during the night; 3 = symptoms causing the patient to be awake most of the night; 4 = symptoms so severe the patient did not sleep) totalling ≥2 on at least 3 of the last 7 consecutive days during the run-in period, and have a mean morning peak expiratory flow rate (PEFR; calculated from the last 7 days of the run-in period) between 50 and 85% of their PEFR measured 15 minutes after administration of salbutamol 400μg at the start of treatment.

Exclusion criteria included: receiving (or having received in the 4 weeks prior to the start of treatment) either salmeterol or any other long-acting inhaled $\beta_2$-agonist; a lower respiratory tract infection within 4 weeks of the run-in period; taking oral, depot or parenteral corticosteroids within 4 weeks of the run-in period, or taking two or more courses of oral, depot or parenteral corticosteroids within 12 weeks of the run-in period; an acute exacerbation of reversible airways obstruction that required hospitalisation within 12 weeks of the run-in period; and a smoking history of 10 pack years (i.e. 10 cigarettes/day for 20 years or 20 cigarettes/day for 10 years or 40 cigarettes/day for 5 years).

### Methods

Patients were assessed at the beginning of the run-in and treatment periods, at 2, 4, 8 and 12 weeks after the start of treatment, and 2 weeks after cessation of treatment. At each of these visits the clinician took three measurements of forced expiratory volume in 1 second ($FEV_1$) and recorded the highest value. Any adverse events reported spontaneously by the patient or as a result of non-suggestive questioning by the clinician were recorded at each clinic visit.

Patients were instructed not to take their medication on the morning of, and to avoid taking rescue medication within 6 hours of, a clinic visit. At these clinic visits systolic and diastolic blood pressure and pulse rate were measured, and the oropharynx was examined for any clinical evidence of candidiasis. At the beginning and end of the treatment period a fasting blood sample was taken (between 0800 and 1000 hours) for biochemical and haematological analysis and the measurement of morning serum cortisol levels.

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; three measurements were made on each occasion and the highest value was recorded in a daily record card. All PEFR measurements were made prior to taking study medication or rescue salbutamol. Patients recorded their use of rescue salbutamol and their daytime and night-time symptom score in the daily record card.

### Data Analysis

Treatment equivalence was determined using the 90% confidence interval (CI) of the difference between the combination and concurrent therapies on mean morning PEFR, weeks 1 to 12 for the intent-to-treat population. For equivalence to be declared the 90% CI had to fall within ±15 L/min. These values were chosen as they have been used

and validated previously in clinical studies[13] and were considered to represent a potential clinically relevant difference.

### Statistical Analysis

All analyses were performed on an intention-to-treat basis. Mean morning PEFR and $FEV_1$ values were analysed 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. Where applicable p-values $<0.05$ were considered to be statistically significant.

## Results

A total of 244 patients (104 males and 140 females) aged from 12 to 78 years (mean age 33 years) were randomised to treatment. The majority of patients (≥75%) had been diagnosed as having asthma for >5 years, while at least 67% had a history of atopy. Of the 244 patients, 121 received combination therapy and 123 concurrent therapy. After randomisation, 35 patients were withdrawn, comprising 18 (15%) from the combination therapy group and 17 (14%) 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 an adverse event (see 'Tolerability' section). Other reasons included: failure to return for follow-up (n = 3), noncompliance (n = 5), and not fulfilling the entry criteria (n = 3).

All 244 patients were included in the analysis of adverse events. The two treatment groups were similar for demographic and baseline characteristics, which are summarised in table I.

Compliance was calculated (as a percentage) using the number of doses used (assessed on the dose counter on the inhalers) divided by the expected use. Compliance was good with both treatments with 91 and 89% of patients in the combination and concurrent therapy groups, respectively, achieving at least 80% compliance during the treatment period. Mean compliance (mean of medication used expressed as a percentage of expected use) was also good in both groups; 94% in

**Table I.** Patient demographics

| Characteristics | Treatment group | |
|---|---|---|
| | salmeterol/fluticasone 50/100μg twice daily | salmeterol 50μg twice daily + fluticasone 100μg twice daily |
| No. of patients | 121 | 123 |
| Gender [no.] (%) | | |
| female | 68 (56) | 72 (59) |
| male | 53 (44) | 51 (41) |
| Mean age [y] (range) | 33 (12-78) | 33 (12-76) |
| Smoking history | | |
| current | 10 (8) | 9 (7) |
| ex-smoker | 24 (20) | 22 (18) |
| never | 87 (72) | 92 (75) |
| Mean baseline PEFR [L/min] (% predicted) | | |
| morning | 368 (83) | 365 (85) |
| evening | 381 (86) | 376 (88) |
| Mean baseline $FEV_1$ [L] (% predicted) | 2.42 (75) | 2.33 (76) |
| Patients using concurrent asthma medication | | |
| methylxanthines | 13 (11) | 7 (6) |
| ipratropium bromide | 4 (3) | 5 (4) |

**$FEV_1$** = forced expiratory volume in 1 second; **PEFR** = peak expiratory flow rate.

**Table II.** Adjusted changes in mean morning and evening peak expiratory flow rate (PEFR) following treatment with either salmeterol/fluticasone 50/100μg twice daily (combination therapy; comb) or salmeterol 50μg twice daily + fluticasone 100μg twice daily (concurrent therapy; conc) over a 12-week period in patients with asthma

| Time | Adjusted change in mean morning PEFR (L/min) | | | | Adjusted change in mean evening PEFR (L/min) | | | |
|---|---|---|---|---|---|---|---|---|
| | comb | conc | difference (90% CI) | p-value | comb | conc | difference (90% CI) | p-value |
| Week 1 | 34 | 30 | –4 (–11, 3) | 0.374 | 30 | 27 | –3 (–10, 5) | 0.561 |
| Week 2 | 36 | 33 | –3 (–11, 6) | 0.610 | 32 | 29 | –3 (–10, 5) | 0.587 |
| Week 3 | 41 | 31 | –10 (–20, –1) | 0.061 | 35 | 31 | –4 (–13, 5) | 0.429 |
| Week 4 | 41 | 31 | –11 (–20, –2) | 0.051 | 36 | 28 | –8 (–17, 1) | 0.135 |
| Weeks 5-8 | 44 | 33 | –12 (–21, –2) | 0.049 | 37 | 30 | –7 (–16, 2) | 0.177 |
| Weeks 9-12 | 47 | 39 | –8 (–19, 3) | 0.220 | 39 | 34 | –5 (–14, 5) | 0.393 |
| Weeks 1-12 | 42 | 33 | –9 (–17, 0) | 0.098 | 36 | 30 | –5 (–13, 2) | 0.241 |

the combination therapy group and 93% in the concurrent therapy group.

### Mean Morning and Evening PEFR

Both treatments improved mean morning PEFR throughout the 12-week treatment period compared with the respective baseline values (mean changes adjusted for baseline were 42 and 33 L/min for combination and concurrent therapy, respectively) [table II]. Over the whole treatment period the difference (90% CI) between the two treatment arms (concurrent-combination) for the increase in mean morning PEFR was –9 L/min (–17, 0 L/min). The 90% CI was outside the defined equivalence interval of ±15 L/min. The difference between the two treatments for mean morning PEFR at the other time periods in the study (weeks 1, 2, 3 and 4, and weeks 5 to 8 and 9 to 12) were similar to that recorded for weeks 1 to 12 (table II).

The mean morning PEFR baseline values were 83 and 85% of the predicted values for the combination and concurrent therapies, respectively, and both treatment arms were found to improve 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 8% for the combination and concurrent therapies, respectively. The weeks 1 to 12 treatment difference (90% CI) was –1% (–3, 1%), and there were no statistically significant differences between the two treatments at any time-point.

Both combination and concurrent therapy improved mean evening PEFR (table II) and the percentage predicted mean evening PEFR during the 12-week treatment period compared with baseline values. At all time-points there were no statistically significant differences in either mean evening PEFR or percentage predicted mean evening PEFR between the two treatment groups.

### $FEV_1$ and Percentage Predicted $FEV_1$

Both combination and concurrent therapy improved $FEV_1$ at each clinic visit during the 12-week treatment period compared with baseline values (adjusted mean changes at week 12 were 0.20 and 0.17L for combination and concurrent therapy, respectively) [fig. 1]. The 90% CI of the treatment difference (–0.03L) of concurrent minus combination therapy at week 12 was –0.12, 0.05L.

The baseline mean $FEV_1$ for the combination and concurrent therapies were 75 and 76% of predicted, respectively, and both improved during treatment (fig. 1). The adjusted mean change from baseline at week 12 was 6% for both therapies; hence the treatment difference was 0%.

### Symptom Scores, Percentage Symptom-Free Days and Nights, and Use of Rescue Salbutamol

Both combination and concurrent therapy increased the number of patients with: a median day-

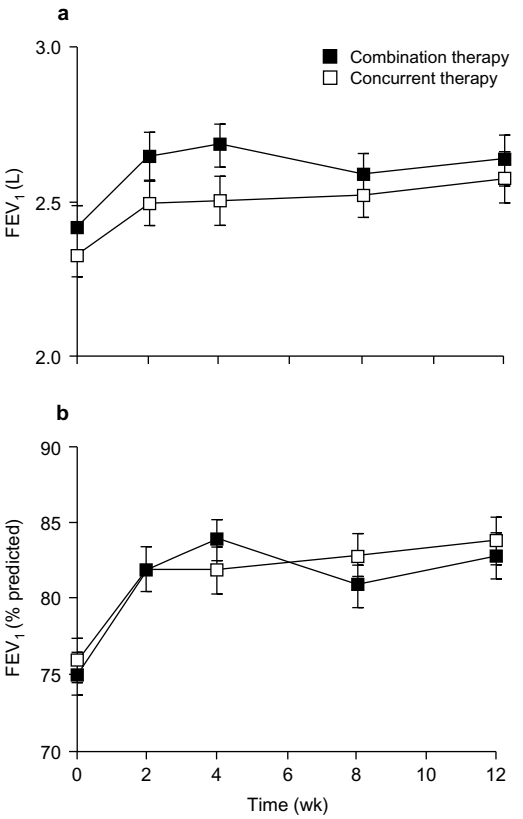


**Fig. 1.** Mean forced expiratory volume in 1 second ($FEV_1$) values and percentage predicted $FEV_1$ values in asthma patients at baseline and following treatment with either salmeterol/fluticasone 50/100μg twice daily (combination therapy) or salmeterol 50μg twice daily + fluticasone 100μg twice daily (concurrent therapy) over a 12-week period.

time symptom score of zero (fig. 2a, table III); a median night-time symptom score of zero (fig. 2b, table III); >75% symptom-free days or nights (table III); and >75% of days or nights when rescue salbutamol was not required (table III). For all of these parameters there were no significant differences between the two treatment groups.

### Tolerability

Overall, both treatment arms were equally well tolerated throughout the 12-week study. A total of 157 patients (88 combination and 69 concurrent therapy) reported an adverse event during treatment. Headaches were more common among patients treated with combination therapy compared with concurrent therapy (12 *vs* 4%, $p = 0.02$), but this was thought to be due to the unusually low incidence of headaches in the concurrent therapy group. Only two patients had headaches considered by the investigator to be drug related, and both were receiving combination therapy.

Eighteen (15%) patients treated with combination therapy and 17 (14%) of those treated with concurrent therapy had an adverse event that was

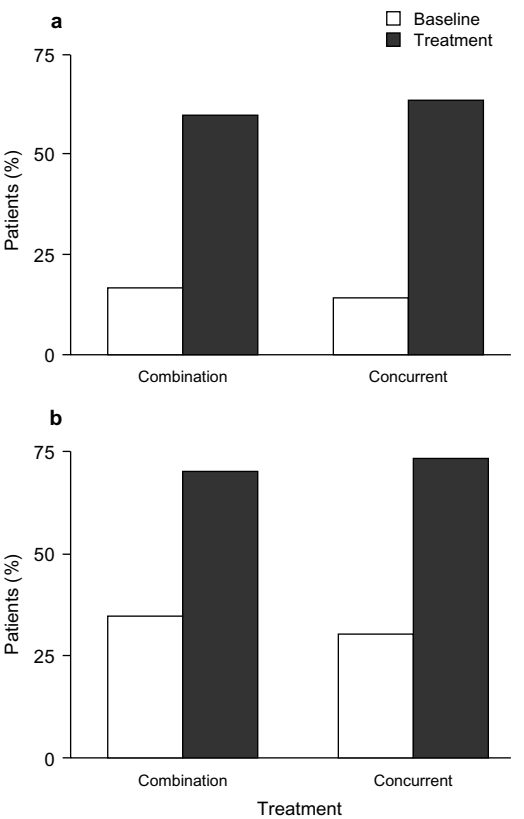


**Fig. 2.** Number of patients (%) with a median (**a**) daytime or (**b**) night-time symptom score of zero at baseline and during 12 weeks' treatment with either salmeterol/fluticasone 50/100μg twice daily (combination therapy) or salmeterol 50μg twice daily + fluticasone 100μg twice daily (concurrent therapy).

**Table III.** Daytime and night-time symptom scores, percentage symptom-free days and nights, and use of rescue salbutamol for asthma patients at baseline and after 12 weeks' treatment with either salmeterol/fluticasone 50/100μg twice daily (combination therapy) or salmeterol 50μg twice daily + fluticasone 100μg twice daily (concurrent therapy)

| | Combination therapy [no. patients (%)] | | Concurrent therapy [no. patients (%)] | |
|---|---|---|---|---|
| | baseline | treatment | baseline | treatment |
| Median daytime symptom score of 0 | 21 (17) | 73 (60) | 18 (15) | 78 (64) |
| Median night-time symptom score of 0 | 42 (35) | 85 (70) | 37 (31) | 89 (74) |
| >75% symptom-free days | 4 (3) | 48 (40) | 4 (3) | 52 (43) |
| >75% symptom-free nights | 19 (16) | 65 (54) | 12 (10) | 69 (57) |
| >75% of days salbutamol not required | 17 (14) | 65 (54) | 24 (20) | 68 (56) |
| >75% of nights salbutamol not required | 43 (36) | 82 (68) | 43 (36) | 87 (72) |

**Table IV.** Number of patients experiencing pharmacologically predictable drug-related adverse events during treatment with either salmeterol/fluticasone 50/100μg twice daily or salmeterol 50μg twice daily + fluticasone 100μg twice daily over a 12-week period

| Adverse event | Treatment group | |
|---|---|---|
| | salmeterol/fluticasone 50/100μg twice daily (%) | salmeterol 50μg twice daily + fluticasone 100μg twice daily (%) |
| Candidiasis (mouth/throat) | 2 (2) | 1 (<1) |
| Candidiasis (nonspecific site) | 0 | 2 (2) |
| Throat irritation | 2 (2) | 3 (2) |
| Hoarseness/dysphonia | 0 | 2 (2) |
| Headaches | 2 (2) | 0 |
| Tachycardia | 0 | 2 (2) |

**Table V.** Geometric mean morning serum cortisol concentrations at baseline and after 12 weeks' treatment with either salmeterol/fluticasone 50/100μg twice daily or salmeterol 50μg twice daily + fluticasone 100μg twice daily

| | Salmeterol/fluticasone 50/100μg twice daily | Salmeterol 50μg twice daily + fluticasone 100μg twice daily |
|---|---|---|
| Baseline cortisol (nmol/L) | 311 | 262 |
| End of treatment cortisol (nmol/L) | 351 | 299 |

considered to be drug related (i.e. judged by the investigator to be almost certainly, probably or possibly related to study medication). The prevalence of pharmacologically predictable adverse events was similar in both treatment groups, and those occurring with a frequency of ≥2% are listed in table IV.

A total of 20 patients withdrew from therapy because of an adverse event [11 (9%) patients treated with combination therapy and 9 (7%) with concurrent therapy]. Seven of these (four combination, three concurrent) were asthma related. Two patients (both combination) were withdrawn as they were pregnant. Overall, there were no differences between the two treatments in adverse events resulting in treatment withdrawal.

No clinically significant changes in laboratory values, physical examinations or vital signs were observed in either treatment group. The geometric mean morning serum cortisol concentrations were similar in the two treatment groups (table V), and were not significantly different between treatments. No differences in frequency of serum cortisol abnormalities between the two treatment groups were noted, and there were fewer patients with abnormalities after treatment than at baseline.

## Discussion

This was the first study to show the clinical effectiveness of salmeterol and fluticasone given in combination (Seretide®) via a single dry powder inhaler (Diskus®) for controlling asthma in patients who remained symptomatic whilst on an inhaled corticosteroid. The beneficial effects of the combination of a long-acting $\beta_2$-agonist and an inhaled corticosteroid are now well established both in the scientific literature[8-12] and in national and international asthma treatment guidelines.[1,2]

The additional clinical benefit of the use of these two classes of drugs in combination is the result of the drugs targeting two different physiological systems involved in the disease process. However, in these studies the two drugs have always been administered via separate inhalers. This study demonstrated that the combination of the two drugs in a single inhaler is at least as effective, and possibly more effective, than the separate administration of the two drugs for controlling asthma.

The primary efficacy variable of this study was mean morning PEFR, and over the 12-week treatment period the treatment difference between the combination and concurrent therapies was outside the criterion for clinical equivalence. Thus, for mean morning PEFR the combination therapy was statistically superior to the concurrent therapy. For the secondary efficacy variables, namely percentage predicted morning PEFR, actual and percentage predicted evening PEFR, $FEV_1$, daytime and night-time symptom scores, percentage symptom-free days and nights, and use of rescue salbutamol, the two therapies had clinically similar effects over the treatment period. The clinical significance of the difference in mean morning PEFR in favour of the combination product is uncertain, although it might result in improved asthma control with this treatment.

Both treatments were well tolerated, and the type and incidence of adverse events were similar for the combination product and the separate administration of the two drugs.

Compliance, calculated using the number of doses used (assessed on the dose counter on the inhalers), was high in both treatment groups (94 and 93% in the combination and concurrent therapies, respectively). Compliance is usually high in clinical trials, as the patients are likely to be highly motivated. A difference in compliance therefore does not appear to be the reason for any differences in efficacy observed in this study.

The combination of salmeterol and fluticasone in a single inhaler results in a device that is convenient, simple to use, and effective, and this might result in improved patient compliance. Studies have shown patient compliance with regular asthma treatment to be variable.[14-19] Coutts et al.[19] examined the effect of inhaled dosage frequency on compliance with therapy and found compliance with a twice-daily dosage frequency was 71%, and that this was reduced to 34% for 3- and 18% for 4-times daily administrations. Thus, the more complicated the dosage regimen the less compliant the patients were, a finding confirmed elsewhere.[20]

The salmeterol/fluticasone combination product will be available in three different dosages, the one reported here (50/100μg) and also 50/250μg and 50/500μg (GlaxoWellcome data on file). Thus, the prescriber will have a choice of dosages available, which should enable asthma control to be achieved independent of the asthma severity of the patient. Moreover, once asthma control is achieved it might be possible to lower the dosage of fluticasone without changing the product.

## Conclusion

In conclusion, this was the first report of the use of a combination of salmeterol and fluticasone in a single inhaler for controlling asthma. The combination product was at least as (and possibly more) clinically effective as the separate administration of the two drugs, was well tolerated and had a satisfactory tolerability profile.

## Acknowledgements

This study was sponsored by GlaxoWellcome Research and Development (SFCB3017).

## References


1. British Thoracic Society. The British Guidelines on Asthma Management. Thorax 1997; 52 Suppl. 1: S1-S21
2. Global strategy for asthma management and prevention. WHO/NHLBI Workshop Report. National Institutes of Health, National Heart, Lung and Blood Institute, Publication Number 95-3659, 1995
3. 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
4. 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 [see comments]. Thorax 1993; 48: 817-23
5. 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
6. Haahtela T, Jarvinen M, Kava T, et al. Comparison of a beta 2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. N Engl J Med 1991; 325: 388-92
7. Juniper EF, Kline PA, Vanzieleghem MA, et al. 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
8. Greening AP, Ind PW, Northfield M, et al. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Allen & Hanburys Limited UK Study Group. Lancet 1994; 344: 219-24
9. Woolcock A, Lundback B, Ringdal N, et al. 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
10. 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
11. 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
12. 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
13. 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
14. Rand CS, Wise RA, Nides M, et al. Metered-dose inhaler adherence in a clinical trial. Am Rev Respir Dis 1992; 146: 1559-64
15. James PN, Anderson JB, Prior JG, et al. Patterns of drug taking in patients with chronic airflow obstruction. Postgrad Med J 1985; 61: 7-10
16. Kinsman RA, Dirks JF, Dahlem NW. Noncompliance to prescribed-as-needed (PRN) medication use in asthma: usage patterns and patient characteristics. J Psychosom Res 1980; 24: 97-101
17. Harding JM, Modell M. How patients manage asthma. J R Coll Gen Pract 1985; 35: 226-8
18. Spector SL, Kinsman R, Mawhinney H, et al. Compliance of patients with asthma with an experimental aerosolized medication: implications for controlled clinical trials. J Allergy Clin Immunol 1986; 77: 65-70
19. Coutts JAP, Gibson NA, Paton JY. Measuring compliance with inhaled medication in asthma. Arch Dis Child 1992; 67: 332-3
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


Correspondence and reprints: Prof. *E.D. Bateman*, Respiratory Clinic, Groote Schuur Hospital, Observatory 7925, Cape Town, South Africa.