Archives of Disease in Childhood 1993; **69:** 206–211

Comparison of the efficacy and safety of inhaled fluticasone propionate 200 μg/day with inhaled beclomethasone dipropionate 400 μg/day in mild and moderate asthma

P Gustafsson, J Tsanakas, M Gold, R Primhak, M Radford, E Gillies

Abstract

This study was designed to compare the efficacy and safety of a new inhaled corticosteroid, fluticasone propionate at a total daily dose of 200 μg, with beclomethasone dipropionate 400 μg/day in childhood asthma. A total of 398 asthmatic children (aged 4–19 years) were randomised to receive either fluticasone propionate 200 μg daily or beclomethasone dipropionate 400 μg daily for six weeks inhaled via a spacer device from a metered dose inhaler. During the study the patients recorded morning and evening peak expiratory flow rate (PEFR), symptom scores, and use of β_2 agonist rescue medication. In addition, clinic visit PEFR and forced expiratory volume in one second were measured. Safety was assessed by recording all adverse events and by performing routine biochemistry and haematology screens including plasma cortisol concentration before and after treatment. For the purposes of analysis the diary card data were grouped into three periods: week 3 (days 15–21), week 6 (days 36–42), and weeks 1–6 (days 1–42). The results showed no significant difference between treatments on most efficacy parameters. However, there were significant differences in changes from baseline in favour of fluticasone propionate for % predicted morning PEFR both at week 3 (fluticasone propionate 6·1%, beclomethasone dipropionate 3·9%) and at week 6 (fluticasone propionate 8·3%, beclomethasone dipropionate 5·9%) and % predicted evening PEFR at week 6 (fluticasone propionate 7·3%, beclomethasone dipropionate 4·9%) and over weeks 1–6 (fluticasone propionate 5·5%, beclomethasone dipropionate 3·6%). Comparison between groups showed that the group receiving fluticasone propionate had a lower % of days with symptom-free exercise at week 6 (fluticasone propionate 87%, beclomethasone dipropionate 81%) and % days without rescue medication at week 6 (fluticasone propionate 87%, beclomethasone dipropionate 80%) and over weeks 1–6 (fluticasone propionate 80%, beclomethasone dipropionate 73%). Except for a higher incidence of sore throat in the fluticasone propionate group, the two treatments did not differ with regard to safety. There was no evidence of adrenal suppression with either treatment. In conclusion, fluticasone propionate 200 μg daily was at least as effective and as well tolerated as beclomethasone dipropionate 400 μg daily in childhood asthma.

(*Arch Dis Child* 1993; **69:** 206–211)

Department of Paediatrics, University Hospital, Linkoping, Sweden
P Gustafsson

Department of Paediatrics, Hippokration Hospital, Thessoloniki, Greece
J Tsanakas

Brampton, Ontario, Canada
M Gold

University of Sheffield, Department of Paediatrics, Children's Hospital
R Primhak

Department of Child Health, Southampton General Hospital
M Radford

Department of Respiratory Medicine, Glaxo Group Research Ltd, Greenford Road, Greenford, Middlesex UB6 0HE
E Gillies

Correspondence to:
Miss Gillies.

Accepted 3 March 1993

Asthma is one of the commonest diseases of childhood, affecting between 11% and 20% of all schoolchildren.[1–3] Asthma reduces the quality of life for children as it leads to growth retardation,[4] inability to exercise,[5] and nocturnal bouts of wheezing resulting in loss of sleep that may also impair daytime concentration at school. In addition, children with more severe disease may be disadvantaged by frequent absences from school. Asthma symptoms experienced by children can exert a psychological stress not only in the affected child but can also be a source of stress for parents.[6] Indeed, because of its prevalence, asthma is one of the most costly items for the public health budget of many countries[7 8] and is likely to cost even more in the future as the incidence is on the increase.[8–10] Therefore, emphasis must be placed on more effective preventative treatment that will improve management of the disease and so the well being of the asthma sufferer.

Inhaled glucocorticosteroid therapy is the recommended treatment for moderate to severe forms of childhood asthma.[11] The systemic side effects commonly associated with oral glucocorticosteroids are largely absent with inhaled corticosteroids at doses up to 400 μg/day. But at doses greater than 400 μg/day, which may be required for the more severe patients, the incidence of systemic side effects is likely to increase.[12] These include suppression of the hypothalamic-pituitary-adrenal axis and the possibility of growth retardation. The use of long term or high dose inhaled corticosteroid treatment is therefore regarded with some caution by parents and paediatricians alike.

Fluticasone propionate is a new inhaled glucocorticosteroid possessing high topical potency and negligible bioavailability.[13] Preliminary studies have shown that fluticasone propionate has approximately twice the potency of beclomethasone dipropionate both as an anti-inflammatory agent[14] and in improving lung function.[15] Furthermore, studies have shown that fluticasone propionate

has negligible oral bioavailability.[13] The lack of systemic action with high oral doses has been demonstrated in healthy volunteers who were treated for 14 days with fluticasone propionate 20 mg/day.[16] These results suggest that fluticasone propionate has a greater local to systemic ratio than beclomethasone dipropionate.

This present study was designed to evaluate fluticasone propionate in the management of childhood asthma by comparing the efficacy and safety of fluticasone propionate 100 μg twice a day with beclomethasone dipropionate 200 μg twice a day.

Patients and methods

PATIENTS

This study involved 398 children aged between 4 and 19 years selected from outpatient clinics at 32 centres in 11 countries worldwide. Each centre obtained ethical permission and patient consent. All children had a history of childhood asthma and were either receiving an inhaled glucocorticosteroid, up to 400 μg/day, or were receiving treatment with a bronchodilator, ketotifen, or sodium cromoglycate but were inadequately controlled. Furthermore, patients who were included had not changed their asthma treatment nor had been admitted to hospital for their respiratory condition during the previous month.

Patients who were not using an inhaled corticosteroid, or who were receiving less than 400 μg daily of their current inhaled corticosteroid, had to demonstrate a need for 400 μg daily based on one of the following criteria established during the run-in period: either, night time symptoms on at least one out of seven consecutive days; or, asthma symptoms on at least three out of seven consecutive days; or, a peak expiratory flow rate (PEFR) <80% of predicted on at least three out of seven consecutive days; or, >15% reversibility of forced expiratory volume in one second (FEV_1) or PEFR after a bronchodilator dose of salbutamol. All patients had to be able to use the pressurised inhaler with a Volumatic (Glaxo) spacer device and a mini-Wright peak flow meter correctly and were able to keep accurate record cards. Patients were excluded if they had received oral corticosteroids in the four weeks before or during the run-in period or on more than three occasions in the preceding three months. Patients were also excluded if they had a lower respiratory tract infection within 14 days of the run-in or if their asthma became unstable during the run-in period.

STUDY DESIGN

This was a double blind, parallel group study. The treatment period lasted six weeks, preceded by a two week run-in period and followed by a two week follow up period. During the two week run-in period, patients continued taking their usual asthma medication at a regular dose with the exception of β_2 adrenoceptor agonist (β_2 agonist) treatment that could be taken at any time to relieve symptoms.

At the end of the run-in, patients discontinued inhaled corticosteroids but all other antiasthma medication was kept constant throughout the study. Eligible patients were randomly allocated to receive treatment with either fluticasone propionate 100 μg twice a day or beclomethasone dipropionate 200 μg twice a day, both administered via a pressurised inhaler and Volumatic spacer device.

ASSESSMENTS

Using the mini-Wright peak flow meter, patients measured their PEFR three times, morning and evening, before taking study medication or using salbutamol. They entered these measurements on a daily record card on which they also noted the severity of their asthma symptoms by day, at night, and on exercise, using four point rating scales. Symptoms during the day were rated from 0=no symptoms to 3=unable to carry out daily activities; symptoms during the night were rated from 0=slept through the night to 3=awake most of the night; and on exercise were scored from 0=not breathless to 3=very breathless, tight chested, and wheezy when walking: unable to run or play games. Patients also recorded their use of the study medication and of the salbutamol inhaler.

Patients attended the clinic on five occasions: at the start of the run-in, at the beginning, middle, and end of treatment, and two weeks after study treatment had finished. At the first clinic visit a full clinical history was documented and a physical examination performed. This was repeated at the end of the treatment period.

At each clinic visit, three measurements of PEFR and FEV_1 were taken before, and 15 minutes after, inhalation of a bronchodilator dose of salbutamol. Where possible, these measurements were made at the same time of day for each visit, preferably in the morning, and the highest value being recorded for each parameter. Patients were asked not to use their bronchodilators for at least four hours before a clinic visit. If this proved impossible, then the use and time of use of the inhaled β_2 agonist was to be recorded on the clinical record form.

The oropharynx was routinely examined at each clinic visit and swabs taken to determine the presence of *Candida albicans* if necessary.

At the beginning and end of the treatment period blood samples were taken for routine haematology and biochemistry and basal plasma cortisol concentration was measured. Where possible, blood samples were taken between 8 am and 10 am and before food.

ANALYSIS

It was estimated that 360 patients providing evaluable data would be required to give the study a power of 90% to detect a mean difference in PEFR of 15 l/min between any two groups. This assumed that significance would be declared at the two sided 5% level. In fact, 398 patients were randomised to treatment. A retrospective analysis performed at the end of

Table 1 Demographic details of the patients randomised to treatment with fluticasone propionate 100 μg twice a day or beclomethasone dipropionate 200 μg twice a day

	Fluticasone propionate (n=197)	*Beclomethasone dipropionate (n=201)*
Male/female	111/86	114/87
White	192	191
Mean (range) age in years	10 (4–19)	11 (4–18)
Mean (SD) height in cm	142 (18)	144 (18)
Mean (SD) weight in kg	39 (16)	41 (17)
Duration of asthma (years)		
<1	5	2
1–5	68	78
6–10	88	77
<10	36	42
No (%) on prestudy asthma medication		
Inhaled β_2 agonist	186 (94)	190 (95)
Oral β_2 agonist	11 (6)	11 (5)
Methylxanthines	17 (9)	32 (16)
Inhaled steroids	142 (72)	125 (62)
Sodium cromoglycate	57 (29)	59 (29)

the study showed that for % PEFR the study had a statistical power of 99% of detecting a 3% difference between treatments.

A baseline was established using data from the daily record cards completed during week 2 of the run-in period. For the treatment period, data were analysed for weeks 1–6 (days 1–42), week 3 (days 15–21), and week 6 (days 36–42). Patients recorded three PEFR measurements every morning and at bedtime before taking study medication. The maximum of the readings was used in the analysis. The mean morning and evening PEFR was then calculated over each period for each patient, and expressed as absolute values and as percentage of predicted values. Predicted lung function values were calculated from sex, age, and height using standard formulas.[17] All statistical analyses were carried out using SAS programs and procedures.

Changes from baseline in diary card PEFRs and changes from baseline in clinic lung function values together with plasma cortisol concentrations (which were previously log transformed) were analysed by analysis of covariance, adjusting for baseline, age, and country. The changes from baseline in percentages of symptom-free days/nights and symptom-free exercise, the median symptom scores and the changes from baseline in use of rescue inhaled β_2 agonist medication and median usage were analysed using the Wilcoxon rank sum test, adjusting according to country using the van Elteren method.[18]

Results

PATIENTS

Table 1 shows the demographic details of the patients randomised to treatment, 197 received fluticasone propionate 100 μg twice a day and 201 received beclomethasone dipropionate 200 μg twice a day. There were no apparent differences between the two treatment groups. The population was predominantly male, white, and atopic (95%) with a mean age of approximately 10 years. Concurrent illnesses and medications were very similar between groups with a large proportion of patients suffering from atopic related diseases.

The two treatment groups were similar with regard to prestudy asthma medication. All patients were using β_2 agonists and over 60% in each group using inhaled corticosteroids. Approximately, 29% of patients in each group were receiving sodium cromoglycate but there were more patients in the beclomethasone dipropionate group receiving methylxanthine preparations (16%) than in the fluticasone propionate group (9%). This pattern of treatment continued into the study period with approximately 22% of patients in both groups taking sodium cromoglycate whereas methylxanthines were taken by 8% and 14% of the fluticasone propionate and beclomethasone dipropionate groups, respectively. No effect of this difference on the results of the study could be determined.

A total of nine patients were withdrawn from the study, four from the fluticasone propionate group and five from the beclomethasone dipropionate group. Reasons for withdrawal were: exacerbations (six patients, three in each group), ineffectiveness of treatment (one patient), did not wish to continue (one patient), and failed to attend (one patient).

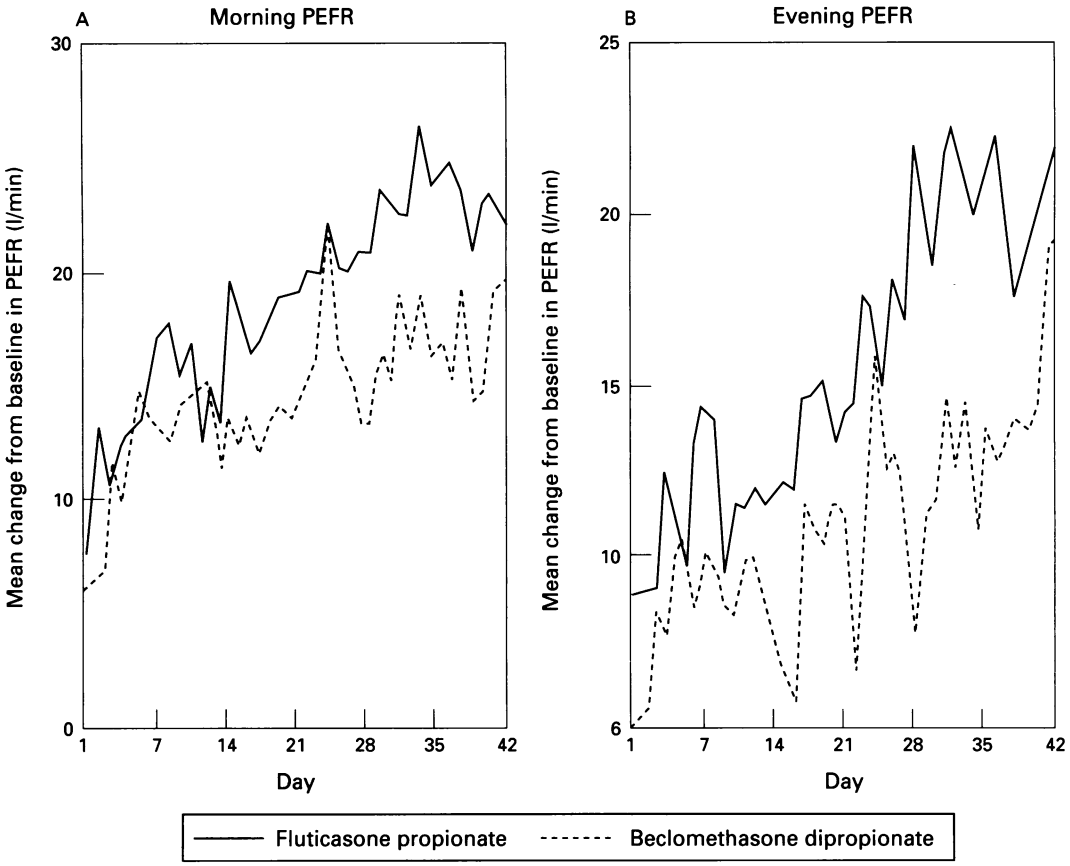
DIARY CARD DATA

Mean morning PEFR increased with each week of treatment for both the fluticasone propionate and beclomethasone dipropionate treatment groups (figure). By the sixth week there was mean improvement of 24 l/min (baseline 318 l/min) in the fluticasone propionate group and 19 l/min (baseline 329 l/min) in the beclomethasone dipropionate group. When converted to percentage predicted values the changes from baseline were statistically significantly different in favour of fluticasone propionate at weeks 3 ($p=0{\cdot}044$) and weeks 6 ($p=0{\cdot}043$; table 2).

Mean evening PEFR showed a similar improvement for both treatment groups (figure). By week 6 patients in the fluticasone propionate group had an increase of 21 l/min above baseline (326 l/min) and patients in the beclomethasone dipropionate group 16 l/min above baseline (340 l/min). When converted to percentage predicted values the changes from baseline in evening PEFR were statistically significantly higher in the fluticasone propionate group than in the beclomethasone dipropionate group at week 6 and over the whole study period (weeks 1–6), $p=0{\cdot}041$ and $p=0{\cdot}034$ respectively (table 2).

Both treatments were similarly effective in reducing diurnal variation in PEFR which was 9 l/min and 10 l/min during the baseline for the fluticasone propionate and beclomethasone dipropionate groups, respectively. The mean change from baseline for week 6 was −4 l/min in the fluticasone propionate group and −3 l/min in the beclomethasone dipropionate group.

There were no statistically significant differences between treatments in the percentage of symptom-free days or nights. During week 6, 83% patients in the fluticasone propionate group, and 81% in the beclomethasone dipropionate group either had no deterioration in daytime asthma symptoms or showed an



The daily mean change from run-in PEFR recorded in the morning (A) and evening (B) while taking fluticasone propionate 200 μg daily or beclomethasone dipropionate 400 μg daily for six weeks.

Table 2 Diary card PEFR data

	No	*Fluticasone propionate*	*Adjusted mean change from baseline**	*No*	*Beclomethasone dipropionate*	*Adjusted mean change from baseline**	*Difference in adjusted means (95% CI)*	*Level of significance (p value)*
Morning PEFR % predicted normal value								
Baseline	196	100·8		201	100·7			
Week 3	193	106·8	6·1	198	104·6	3·9	2·2 (0·1 to 4·4)	0·044
Week 6	185	108·8	8·3	195	106·5	5·9	2·4 (0·1 to 4·7)	0·043
Weeks 1–6	196	106·8	6·2	201	105·0	4·5	1·7 (−0·1 to 3·5)	0·069
Evening PEFR % predicted normal value								
Baseline	196	103·6		201	103·9			
Week 3	194	108·5	5·0	198	106·9	3·0	1·9 (−0·2 to 4·1)	0·080
Week 6	183	110·6	7·3	193	108·4	4·9	2·4 (0·1 to 4·7)	0·041
Weeks 1–6	196	109·0	5·5	201	107·2	3·6	1·9 (0·1 to 3·7)	0·034

*Means adjusted for baseline, age, and country. CI=confidence intervals.

improvement. Similarly, at week 6, 83% of patients receiving fluticasone propionate and 82% of patients receiving beclomethasone dipropionate had no deterioration or showed an improvement in night time asthma symptoms. There was however, a significant difference between treatments in the percentage of days with symptom-free exercise. At week 6, more patients on fluticasone propionate showed no deterioration or enjoyed more symptom-free exercise days (87%) than patients using beclomethasone dipropionate (81%; p=0·04, scores stratified by region).

Daytime and night time asthma scores were comparable. A total of 90% of patients receiving fluticasone propionate and 93% of patients receiving beclomethasone dipropionate had a median daytime symptom score of 0 or 1 during the run-in and at week 6; and 93% of patients receiving fluticasone propionate and 96% of patients receiving beclomethasone dipropionate had a median night time symptom score of 0 or 1 during the run-in and at week 6. Exercise asthma symptom scores were also comparable, 91% of patients using fluticasone propionate and 94% of patients using beclomethasone dipropionate had a median asthma symptom score of 0 or 1 during the run-in at week 6.

A greater number of patients in the fluticasone propionate group than in the beclomethasone dipropionate group had an increase in the percentage of rescue β_2 agonist free days. This was statistically significant at week 6 (fluticasone propionate 87%, beclomethasone dipropionate 80%; p=0·01) and over the whole treatment period (fluticasone propionate 80%, beclomethasone dipropionate 73%; p=0·046). Use of rescue medication per day also varied at week 6 when a greater number of patients in the fluticasone propionate group (87%) showed an improvement over baseline compared to beclomethasone dipropionate (84%; p=0·044).

CLINIC LUNG FUNCTION

For both treatments, the adjusted mean change from baseline in clinic lung function

Table 3 Clinic lung function

	No	Fluticasone propionate (% predicted)	Adjusted mean change from baseline*	No	Beclomethasone dipropionate (% predicted)	Adjusted mean change from baseline*	Significance level of difference in adjusted means
PEFR (l/min)							
Baseline	192	325 (102·2)		198	328 (100·7)		NS
Week 3	192	344 (108·5)	20	198	344 (104·6)	17	NS
Week 6	193	343 (108·1)	20	195	350 (107·4)	21	NS
FEV_1 l							
Baseline	190	2·08 (88·9)		198	2·10 (87·8)		NS
Week 3	190	2·20 (93·8)	0·11	198	2·21 (92·2)	0·11	NS
Week 6	190	2·19 (94·1)	0·12	193	2·26 (94·1)	0·15	NS

*Means adjusted for baseline, age, and country. NS=not statistically significant.

was similar before and after bronchodilator usage. At the end of the treatment period for patients using fluticasone propionate, the change from baseline in PEFR was 20 l/min and for those using beclomethasone dipropionate, 21 l/min. The change from baseline in FEV_1 was 0·12 l for the fluticasone propionate group and 0·15 l for the beclomethasone dipropionate group (table 3). After bronchodilator the PEFR increased from baseline by 15 l/min for the fluticasone propionate group and 12 l/min for the beclomethasone dipropionate group and the FEV_1 increased from baseline by 0·07 l for the fluticasone propionate group and 0·10 l for the beclomethasone dipropionate group.

SAFETY ASSESSMENT

During the six week treatment period 99 patients (50%) reported 155 adverse events with fluticasone propionate and 95 patients (47%) reported 153 adverse events with beclomethasone dipropionate. Three patients on fluticasone propionate and two patients on beclomethasone dipropionate had serious adverse events, and three patients in each treatment group withdrew because of adverse events (exacerbation of asthma).

The most commonly occurring (>5%) adverse events were upper respiratory tract infection, asthma and related events, rhinitis, and sore throat (table 4). Apart from the incidence of sore throat reported by 16 patients (8%) on fluticasone propionate but only by two patients (<1%) on beclomethasone dipropionate, there were no significant differences between the groups. Although there was a significant ($p<0·001$) difference in the incidence of sore throat between the groups, the majority of reports were related to pharyngitis and tonsillitis and were not linked to hoarseness. The incidence of hoarseness and oral candidiasis, which are pharmacologically predictable adverse events common to inhaled corticosteroid treatment, was low. Hoarseness was reported by two patients in each treatment group and oral candidiasis was reported by three patients on beclomethasone dipropionate and none on fluticasone propionate.

Table 4 Most common (>5%) and pharmacologically predictable adverse events

Adverse event	Fluticasone propionate (n=197)	Beclomethasone dipropionate (n=201)
Upper respiratory tract infection (%)	29 (15)	32 (16)
Asthma and related events (%)	18 (9)	23 (11)
Sore throat (%)*	16 (8)	2 (<1)
Rhinitis (%)	9 (5)	13 (6)
Oral candidiasis (%)†	0	3 (1)
Hoarseness (%)†	2 (1)	2 (<1)

*Statistically significantly different between treatments ($p<0·001$).
†Pharmacologically predictable adverse events.

There were no clinically significant changes in either haematological or biochemical variables.

CORTISOLS

There was no significant difference between the two treatments in the effect on hypothalmic-pituitary-adrenal axis function; ratio of fluticasone propionate:beclomethasone dipropionate was 1·00, 95% confidence interval 0·91 to 1·09, $p=0·989$. The geometric mean cortisol concentration was 196 nM during the run-in and 214 nM on fluticasone propionate treatment (n=182) and 217 nM during run-in and 228 nM on beclomethasone dipropionate (n=181). There was no apparent difference in the numbers of patients who had a cortisol value below the lower normal limit before and after treatment. In the fluticasone propionate group 19/191 (10%) had a low cortisol concentration at baseline and 16/188 (9%) after treatment and in the beclomethasone dipropionate group 12/191 (6%) had a low cortisol value at baseline and 8/191 (4%) after treatment.

VITAL SIGNS

No significant changes in weight, pulse rate, or systolic or diastolic blood pressure were detected.

Discussion

Current international guidelines from paediatricians recommend the use of prophylactic treatments such as inhaled corticosteroids in moderate childhood asthma.[11] However, there is still reluctance[19 20] to use these drugs in children because of the possibility of serious adverse effects even with conventional doses.[21–23] This 'corticosteroid fear' is supported by the fact that only about 20% of an inhaled dose of the drug reaches the airways, the rest is swallowed.[24] After it is swallowed this large fraction of drug (approximately 80%) may contribute to systemic steroid effects. The use of spacer devices with metered dose inhalers do enhance lung deposition while lessening oropharyngeal deposition and systemic absorption. Nevertheless, an ideal inhaled corticosteroid should have a wide margin between local and systemic activity.

Studies so far, suggest that fluticasone propionate is such a compound.[13–16 25] Due to very low oral absorption and extensive first pass hepatic metabolism to an inactive metabolite, fluticasone propionate has been shown to have negligible oral bioavailability.[13] Moreover, in preclinical and clinical studies in adults, when compared with beclomethasone dipropionate, fluticasone propionate is approximately twice as potent.[14 15]

This present study confirms the previous findings. The results presented here have demonstrated that fluticasone propionate 100 μg twice a day is at least as effective as beclomethasone dipropionate 200 μg twice a day in childhood asthma. Similar improvements in lung function were seen on both treatments and when converted to percentage predicted values, PEFR was statistically significantly greater on fluticasone propionate than on beclomethasone dipropionate treatment. Asthma symptoms were reported by few patients and there were statistically significantly more patients who enjoyed symptom-free exercise days in the fluticasone propionate group than the beclomethasone dipropionate group. Patients using fluticasone propionate also required less relief bronchodilator medication than those using beclomethasone dipropionate.

There were no unexpected findings in the adverse event profile of fluticasone propionate, the most commonly reported events being related to the patients' asthma. The incidence of all adverse events was low, and with the exception of sore throat, there was no difference between the treatments. There were more reports of sore throat (8%) during fluticasone propionate treatment than during beclomethasone dipropionate treatment (<1%). This may be related to tonsillitis and pharyngitis as it has not been reported in any other studies. In fact, the incidence of expected pharmacologically predictable adverse events, that is candida and hoarseness, was not marked and not different between the two treatments. This may have been as a consequence of the use of spacer devices which limits oropharyngeal deposition. However, a study using high doses (750–1500 μg/day) of fluticasone propionate in adults has shown that the majority of adverse events reported were unrelated to the inhaled corticosteroid.[25]

Analysis of haematological and biochemical variables in this study revealed no clinically significant abnormalities during either treatment. Furthermore, there was no evidence of hypothalmic-pituitary-adrenal axis suppression, as assessed by basal plasma cortisol values, with either treatment.

The patients studied had mild or moderate asthma as can be judged from their lung function parameters and symptom scores at baseline. Nevertheless, the confirmation of the 2:1 potency relationship between fluticasone propionate and beclomethasone dipropionate in childhood asthma is valid as all differences in efficacy found were in favour of fluticasone propionate.

To conclude, at the doses chosen, fluticasone propionate is approximately twice as potent as beclomethasone dipropionate in the management of mild to moderate childhood asthma with a similar safety profile.

We would like to express thanks to the following for their assistance with the study: Dr D E Baets, Professor D Baran, Dr J Leclercq-Foucart (Belgium); Dr G Rivard, Dr S Spier, Dr B Zimmerman, Dr J Dolovich, Dr S Lavi, Dr S Feanny (Canada); Dr M M Marenk, Dr P R Rantanen (Finland); Dr J B G Watson, Dr M Taylor, Dr D F Lillis (Ireland); Professor A Boner, Professor M de La Rosa, Professor M Miraglia del Guidice, Dr L Longo (Italy); Dr J Vermeulen, Dr D Cohen (South Africa); Dr H Hildebrand, Dr T Berg, Dr C Moller, Dr G Hedlin (Sweden); Dr J L Y Yntema (Switzerland); Dr B McCord, Dr R C Groggins, Dr B H Davies, Dr R Gregson (United Kingdom); Professor D Berdel, Dr W Lassig (Germany).

1 Williams HB, McNicol KN. Prevalence, natural history, and relationship of wheezy bronchitis and asthma in children. An epidemiological study. *BMJ* 1969; iv: 321–5.
2 McNicol KN, Williams HB. Spectrum of asthma in children – I. Clinical and physiological components. *BMJ* 1973; iv: 7–11.
3 McNicol KN, Williams HB. Spectrum of asthma in children – II. Allergic components. *BMJ* 1973; iv: 12–6.
4 Hauspie R, Susanne C, Alexander F. Maturational delay and temporal growth retardation in asthmatic boys. *J Allergy Clin Immunol* 1977; **59:** 200–6.
5 Couglin SP. Sport and the asthmatic child: a study of exercised induced asthma and the resultant handicap. *J R Coll Gen Pract* 1988; **38:** 253–5.
6 Anderson HR, Bailey PA, Cooper JS. Morbidity and school absence caused by asthma and wheezing illness. *Arch Dis Child* 1983; **58:** 777–84.
7 Anderson HR. Epidemiology of asthma. *Br J Hosp Med* 1992; **47:** 99–104.
8 Action Asthma. *The occurrence and cost of asthma*. Worthing: Cambridge Medical Publications, 1990.
9 Evans R III, Mullally DI, Wilson RW. National trends in the morbidity and mortality of asthma in the US: prevalence, hospitalization, and death from asthma over two decades: 1965–1984. *Chest* 1987; **91** (suppl): 65–74S.
10 National Heart, Lung and Blood Institute, National Asthma Education Program, Expert Panel Report. Guidelines for the diagnoses and management of asthma. *J Allergy Clin Immunol* 1991; **88** (3): part 2.
11 Warner JO, Gotz M, Landau LI, *et al.* Management of asthma: a consensus statement. *Arch Dis Child* 1989; **64:** 1065–79.
12 Priftis K, Milner AD, Conway E, Honour JW. Adrenal function in asthma. *Arch Dis Child* 1990; **65:** 838–40.
13 Harding SM. The human pharmacology of fluticasone propionate. *Respir Med* 1990; **84** (suppl A): 25–9.
14 Phillips GH. Structure-activity relationships of topically active steroids: the selection of fluticasone propionate. *Respir Med* 1990; **84** (suppl A): 19–23.
15 Svendsen UG. Fluticasone propionate (a new inhaled steroid): clinical developments in mild to moderate adult asthmatics. *Eur Respir J* 1990; 3 (suppl 10): 250s (abstract).
16 Harding SM. Human pharmacology of fluticasone. *Allergologie* 1989; **12:** 77 (abstract).
17 Polgar G, Promadhat V. *Pulmonary function testing in children: techniques and standards*. Philadelphia: WB Saunders, 1971.
18 Van Elteren PH. On the combination of independent two sample tests of Wilcoxon. *Bulletin of the International Statistical Institute* 1960; **37:** 353–61.
19 Larson GL. Asthma in children. *N Engl J Med* 1992; **326:** 1540–5.
20 Reed CE. Aerosol steroids as primary treatment of mild asthma. *N Engl J Med* 1991; **325:** 425–6.
21 Littlewood JM, Johnson AW, Edwards PA, Littlewood AE. Growth retardation in asthmatic children treated with inhaled beclomethasone dipropionate. *Lancet* 1989; i: 115–6.
22 Wyatt R, Waschek J, Weinburger M, Sherman B. Effects of inhaled beclomethasone and alternate-day prednisone on pituitary-adrenal function in children with chronic asthma. *N Engl J Med* 1978; **299:** 1387–92.
23 Law CM, Marchant JL, Honour JW, Preece MA, Warner JO. Nocturnal adrenal suppression in asthmatic children taking inhaled beclomethasone dipropionate. *Lancet* 1986; i: 924–44.
24 Davies DS. Pharmacokinetics of inhaled substances. *Postgrad Med J* 1975; **51** (suppl 7): 69–75.
25 Bauer K, Bantje TA, Sips AP, *et al.* The effects of inhaled fluticasone propionate (FP); a new potent corticosteroid in severe asthma. *Eur Resp J* 1988; **1** (suppl 2): P201s (abstract).