Fluticasone propionate 750 µg/day versus beclomethasone dipropionate 1500 µg/day: comparison of efficacy and adrenal function in paediatric asthma

Dominic Fitzgerald, Peter Van Asperen, Craig Mellis, Mareea Honner, Lucia Smith, Geoffry Ambler

Abstract

***Background*—Previous studies have suggested a 2:1 efficacy advantage of fluticasone propionate (FP) over beclomethasone dipropionate (BDP) in adults on high dose inhaled steroids and children on low dose inhaled steroids. The lower doses of FP required to provide equivalent efficacy to BDP also appear to have fewer systemic effects as measured by adrenal function.**

***Methods*—The efficacy and safety of FP 750 µg/day and BDP 1500 µg/day were compared in 30 children with persistent asthma (requiring 1000–2000 µg/day of inhaled corticosteroids) in a 12 week randomised double blind crossover study. Medication was delivered by a spacer device in two divided doses. Primary efficacy variables were peak expiratory flows (PEF). Adrenal function was assessed by 24 hour urinary free cortisol levels at eight and 12 weeks and ACTH and low dose synacthen tests (LDST) at 12 weeks. The results were adjusted for sequence and period differences.**

***Results*—There was no difference in the primary efficacy variables over the two 12 week treatment periods (difference in adjusted means for morning PEF 1.3 l/min (95% CI –6.1 to 8.8), p = 0.112) and symptom scores (cough, tachypnoea, wheeze, shortness of breath; difference in adjusted means of night time scores: –0.06 (95% CI –0.14 to 0.03); p = 0.136). Similar degrees of mild adrenal dysfunction were found during BDP and FP treatment phases. Identical height gain velocities were shown during the corresponding periods.**

***Conclusions*—FP 750 µg/day is as effective as BDP 1500 µg/day in children with persistent asthma. At these very high doses we were unable to demonstrate a safety advantage of FP over BDP as assessed by adrenal function. However, measures of adrenal function may have been influenced by concurrent and previous systemic steroid usage, and possibly by effects of disease activity.**

(*Thorax* 1998;**53**:656–661)

Keywords: adrenal function; asthma; beclomethasone; fluticasone; randomised trial

Royal Alexandra Hospital for Children, P O Box 3515, Parramatta, Sydney, New South Wales, Australia 2124
D Fitzgerald
P Van Asperen
C Mellis
M Honner
L Smith
G Ambler

Correspondence to:
Dr D Fitzgerald, Department of Paediatrics, John Hunter Children's Hospital, Locked Bag No. 1, Newcastle Mail Centre, Newcastle, New South Wales, Australia 2310.

Received 24 September 1997
Returned to author
12 December 1997
Revised manuscript received
10 March 1998
Accepted for publication
8 April 1998

Inhaled corticosteroids are currently considered to be the most effective anti-inflammatory therapy for patients with asthma requiring preventive therapy[1] but there remains some controversy about their potential for systemic toxicity, particularly in children.[1–4] However, in children with persistent asthma this potential for side effects needs to be balanced against the morbidity from poorly controlled asthma.[2–5]

Fluticasone propionate (FP), a recently introduced inhaled corticosteroid, has negligible oral bioavailability.[6] While this leads to less systemic activity from gastrointestinal absorption, this may be offset by pulmonary absorption of a drug with greater potency.[7] A study in adults has shown that high dose FP (1500 µg/day) is more effective than beclomethasone dipropionate (BDP) in a dose of 1500 µg/day without any increase in systemic side effects.[8] In addition, FP (1000 µg/day) has been shown to be as effective as BDP (2000 µg/day) with less evidence of adrenal suppression with FP based on plasma cortisol estimation.[9] In children this 2:1 efficacy ratio of FP over BDP has been confirmed in low doses (FP 200 µg/day versus BDP 400 µg/day) without any evidence of adrenal suppression on either treatment.[10] To date, however, studies of children on high dose inhaled steroids (≥1000 µg/day) have not been performed.

In this study we compared the efficacy and safety of FP 750 µg/day and BDP 1500 µg/day in children with persistent asthma who had required 1000–2000 µg/day of inhaled steroid over the previous 12 months for adequate control of their asthma.

Methods

STUDY DESIGN

This was a single centre randomised double blind crossover study. School age children (5–16 years) with persistent severe asthma were enrolled. Persistent severe asthma was defined as asthma requiring 1000–2000 µg/day of inhaled corticosteroid (BDP or budesonide (BUD)) continuously for symptom control over the previous 12 months. We included children who had required up to six short courses of systemic corticosteroids (<7 days of prednisone 1–2 mg/kg/day) in the preceding year. Eligible patients entered a four week run in period on open label BDP 1500 µg/day (given as a twice daily dose) to ensure stability and optimise inhaler technique. After the run in period patients were randomised to receive

either FP 750 μg/day or BDP 1500 μg/day delivered in a twice daily dose via a metered dose inhaler (MDI) and a large volume (750 ml) spacer. Patients were allocated to treatment order (FP-BDP or BDP-FP) according to a randomisation list (in blocks of four) produced prior to the commencement of the study. After 12 weeks of treatment patients crossed over to the other steroid treatment for a further 12 weeks. There was no washout period between the two treatment phases because of the severity of the asthma.

Patients were permitted the use of short and long acting β agonists, cromoglycate, or theophylline as prescribed prior to entry to the study and asthma exacerbations were treated in the same way as previously. In school aged children we felt it unlikely that an accurate record of MDI usage could be maintained for the study duration (seven months) and that any significant asthma exacerbation in moderately severe asthmatics would progress to nebulised therapy. Consequently, an exacerbation of asthma was defined as any event requiring nebulised salbutamol or systemic corticosteroids.

The study was approved by the ethics review committee of the Royal Alexandra Hospital for Children. Written informed consent was obtained from parents prior to enrolment.

ASSESSMENT OF CLINICAL RESPONSE

Patients kept a daily symptom diary card for daytime symptoms and night time symptoms and recorded all medications taken for the duration of the study. Daytime symptoms were recorded each evening: 0 = no symptoms, 1 = wheezing, cough on strenuous exercise and/or hurrying; 2 = wheezing, cough or shortness of breath (SOB) most of the day with limitation of normal activities; 3 = unable to carry out normal activities because of SOB. Similarly, nighttime symptoms were recorded each morning: 0 = no symptoms; 1 = symptoms caused waking once or early; 2 = awoken two or three times by cough, wheeze, SOB, asthma; 3 = awake most of the night with cough, wheeze, SOB, asthma. Each morning and evening patients recorded the highest of three peak expiratory flow (PEF) manoeuvres using a mini-Wright peak flow meter (Clement Clarke International, London, UK). Patients were seen every four weeks when spirometric values (pre and post 400 μg salbutamol delivered via MDI and large volume spacer), height (measured at the same time of day), weight, blood pressure and heart rate were measured. Subjects were required to withhold long acting β_2 agonists for 12 hours and short acting β_2 agonists for four hours prior to spirometric testing and scheduled clinical reviews.

ASSESSMENT OF ADRENAL FUNCTION

Urine was collected for measurement of 24 hour cortisol excretion prior to clinic visits after eight and 12 weeks on each steroid. Low dose synthetic ACTH (synacthen) cortisol stimulation tests (LDST)[11 12] were performed at the end of each 12 week treatment phase. Patients were fasted from midnight prior to undertaking the LDST at 08.00 hours. Sixty minutes prior to venepuncture topical local anaesthetic patches (Astra Draco, Lund, Sweden) were applied to the patients' cubital fossae by a parent. An indwelling peripheral 22 gauge venous catheter was sited through the anaesthetised skin. The LDST consisted of a basal morning serum ACTH and cortisol (08.00 to 09.00 hours) collected prior to the intravenous injection of synacthen (0.5 μg/1.73 m^2 body surface area). Serum cortisol levels were measured 30 and 60 minutes later. The LDST has been reported to be a more sensitive discriminator of mild adrenal dysfunction in both adults and children.[11 12] We used the normal ranges proposed by Broide *et al*[12]—namely, baseline cortisol $\geqslant$200 nmol/l and LDST stimulated cortisol $\geqslant$500 nmol/l.

ASSESSMENT OF GROWTH

Height was measured at each visit by the same observer using a stadiometer and expressed as height standard deviation score (Ht SDS), according to the National Center for Health Statistics (NCHS) standards.[13]

STATISTICAL ANALYSIS

Sample size calculation for efficacy data was based on the assumption that a 5% difference in mean daily PEF (15 l/min in 10 year old children) was a clinically relevant difference between treatment groups and for an alpha error of 5% and a beta error of 10% (power = 90%). We calculated the sample size using the standard deviation of the previously demonstrated difference between repeated measurements of PEF to be 17 l/min.[14] This gave an effect size of 0.88, necessitating 30 patients in a crossover design. This sample size was also sufficient to demonstrate a clinically relevant difference between cortisol responses after a short synacthen test of 200 nmol/l (1 standard deviation)[15] with an alpha error of 5% and a beta error of 10%. To compare the two medications a full covariance model was used with age, sex, and sequence effects included as between patient covariates. A combination of multivariate repeated measures and conventional crossover methods was used for analyses of the main outcome and safety (cortisol) variables. Results are expressed as mean (SD) or mean (95% confidence intervals (95% CI)). Means for comparison of treatments were adjusted for final analysis because of a significant period effect and patient differences in sequence groups.

Results

STUDY SAMPLES AND WITHDRAWALS

Thirty four subjects were enrolled in the run in period. Twenty (59%) had received budesonide 1200–1600 μg/day and 14 (41%) had received BDP 1000–2000 μg/day continuously for the preceding 12 months. Prior to study entry 12 of the 34 subjects (35%) were using salmeterol (long acting β_2 agonist). All subjects were randomised to either FP-BDP or BDP-FP treatment sequences. For patients in the treatment sequences there were no differences in the mean (SD) duration of asthma treatment (FP-BDP: 8.7 (2.2) years versus

Table 1 Demographic characteristics of the basic efficacy sample comparing the two sequence groups: FP-BDP vs BDP-FP. There were no significant differences between the sequence groups

	Basic efficacy sample (n=30)	*FP-BDP (n=16)*	*BDP-FP (n=14)*
Age (years)	Mean (SD)	10.5 (2.5)	9.4 (2.9)
	Range	6–15	5–13
Sex		13 male; 3 female	6 male; 8 female
Height (cm)	Mean (SD)	142.1 (11.8)	136.0 (17.9)
	Range	120–167	99–163
Weight (kg)	Mean (SD)	38.7 (11.3)	36.2 (14.4)
	Range	24–62	17–66
Baseline	Mean (95% CI)	1.93 (1.71 to 2.06)	1.75 (1.59 to 1.93)
FEV_1 (l)	Percentage predicted (95% CI)	86 (82 to 90)	86 (82 to 90)
Baseline	Mean (95% CI)	319 (288 to 348)	294 (262 to 326)
PEF (l/min)	Percentage predicted (95% CI)	101 (94 to 108)	105 (98 to 112)

FEV_1 = forced expiratory volume in one second; PEF = peak expiratory flow.

BDP-FP: 7.4 (2.9) years; p = 0.150), the history of other atopic manifestations including eczema, hayfever, and rhinitis (10/17 versus 13/17; p = 0.463), or the number of admissions to hospital (range 0–4) for asthma in the preceding year (χ^2 = 0.869 for 1 df, p = 0.351). Twenty of the 34 subjects (59%) had not been hospitalised in the preceding 12 months.

Thirty subjects (88.2%) completed the study. Four patients were withdrawn (two from each treatment sequence). This was because of non-compliance in two cases (one from each treatment sequence during the first 12 weeks) and parental request in one case (behaviour deterioration coinciding with commencing school). The attending physician requested withdrawal in the other case because of deterioration in asthma control necessitating three courses of oral corticosteroids within one month. There were no significant differences in withdrawal rates between treatments, study phases, or treatment sequence groups.

As this study was analysed on an "intention to treat" basis[16] the sample considered for all analyses of efficacy and safety was the total sample of 34 patients. However, for a crossover design, data from both treatment phases are required for comparative analyses. Thus, a basic efficacy sample was formed by excluding the four withdrawn patients. Three patients declined venepunctures, so assessment of their HPA axis was limited to 24 hour urinary free cortisol (UFC) levels. Consequently, the sample size for assessment of the LDST was 27. As oral corticosteroids may alter endogenous cortisol levels, a subgroup analysis was defined for those 17 subjects who did not take oral corticosteroids during the study. There were no significant differences for any of the demographic, efficacy, or safety variables irrespective of whether analysed by intention to treat or the basic efficacy sample.

Table 2 Primary efficacy variables (n = 30)

	PEF		*Symptoms*	
	AM	*PM*	*Day*	*Night*
FP (adj mean)	311	316	0.3	0.3
BDP (adj mean)	308	312	0.4	0.3
Diff (adj mean)	2.6	4.2	−0.1	−0.05
(95% CI)	(−1.8 to 7.0)	(−1.2 to 9.5)	(−0.8 to 0.02)	(−0.14 to 0.03)

There were no significant differences between treatments for peak expiratory flow (PEF) rates or symptom scores.

BASIC EFFICACY SAMPLE

The characteristics of the efficacy sample are summarised in table 1. There were differences in the two sequence groups. There were 14 patients in the BDP-FP sequence group and 16 patients in the FP-BDP sequence group. A female preponderance occurred in the BDP-FP sequence group (59% female) while a male preponderance occurred in the FP-BDP sequence group (82% male). Exacerbations were also more common in the BDP-FP sequence group occurring in 12 of the 14 subjects (85.7%) compared with nine of the 16 subjects (56.2%) in the FP-BDP sequence group. There were 52 exacerbations in the BDP-FP group compared with 16 in the FP-BDP sequence group (p<0.001); however, similar numbers of exacerbations occurred whilst receiving FP and BDP. Absolute lung function was higher in the FP-BDP sequence group but neither absolute nor percentage predicted lung function was significantly different between the sequence groups. There was a significant period effect noted for both sequence groups with an increase in asthma exacerbations and decline in lung function during the second treatment phase. Salmeterol was used in nine of the 30 subjects (35%) in the efficacy sample (four FP-BDP and five BDP-FP; p = 0.404). There were no differences in the duration of asthma, presence of atopy, number of exacerbations of asthma requiring admission to hospital, age, height, weight, FEV_1, or PEF between those using salmeterol and those not using salmeterol. Means were adjusted for final analysis to account for the sequence differences and the period effect.

PRIMARY EFFICACY VARIABLES

The daily mean morning and evening PEF and day and night symptoms scores over the three month period are presented in table 2, adjusted for sequence differences and period effect. Although the trend favoured FP, there was no statistically significant difference in these parameters between FP and BDP treatment periods. To investigate a possible carryover effect the analysis was repeated for the last month (month 3) of treatment but again no difference could be demonstrated between treatment groups.

SECONDARY EFFICACY VARIABLES

There was no difference in physician or patient/parent assessments of efficacy with 90% of both rating FP and BDP effective or very effective. The total number of exacerbations (FP = 33; BDP = 35) and those exacerbations requiring systemic steroids (FP = 9; BDP = 11) were also not different between FP and BDP treatment periods. However, there were only 16 exacerbations in total for the FP-BDP group, while there were 52 exacerbations in the smaller BDP-FP group. This difference in incidence was highly significant (p<0.001), suggesting that, by chance, randomisation had placed a higher proportion of less stable cases in the BDP-FP sequence. In addition, there was a difference between phases for 57% of the patients, and these tended to

Table 3 Adrenal function for all subjects

	UFC (nmol/24 h)		*ACTH (pmol/l)*	*LDST (nmol/l)*	
	8 wks (n=28)	*12 wks (n=25)*	*(n=26)*	*Baseline (n=27)*	*Peak (n=27)*
FP (adj mean)	25.0	25.3	7.21	265	437
BDP (adj mean)	23.3	25.2	7.18	246	436
Diff (adj mean)	1.7	0.1	0.03	18.65	1.15
(95% CI)	(−3.7 to 7.2)	(−6.0 to 6.3)	(−1.59 to 1.65)	(−39.6 to 76.9)	(−45.79 to 48.09)

UFC = urinary free cortisol; ACTH = adrenocorticotrophin; LDST = low dose cortisol stimulation test.

Table 4 Adrenal function for the subset of patients who did not receive oral steroids during the study

	UFC (nmol/24 h)		*ACTH (pmol/l)*	*LDST (nmol/l)*	
	8 wks (n=18)	*12 wks (n=18)*	*(n=16)*	*Baseline (n=17)*	*Peak (n=17)*
FP adj mean	23.4	23.3	9.36	252.85	432.02
BDP adj mean	20.9	28.4	7.67	230.03	407.16
Diff adj mean	2.5	−5.1	1.69*	22.82	24.86
(95% CI)	(−5.5 to 10.5)	(−12.6 to 2.4)	(0.08 to 3.29)	(−37.63 to 83.27)	(−32.32 to 82.04)

*p<0.04.
UFC = urinary free cortisol; ACTH = adrenocorticotrophin; LDST = low dose cortisol stimulation test.

have fewer exacerbations in the first phase, regardless of treatment. The period effect was significant (p = 0.015) but the treatment difference was not significant (p = 0.476). Interestingly, when the number of subjects who required oral corticosteroids to treat exacerbations of asthma was used as an indicator of asthma lability, no significant differences were demonstrated (FP-BDP: 4/16 versus BDP-FP 8/14; χ^2 = 2.015 for 1 df; p = 0.156). Similarly, the total number of courses of oral steroids did not differ between groups (FP-BDP 7/16 versus BDP-FP 13/14; χ^2=0.272 for 1 df; p = 0.10). Additionally, mean clinic PEF (FP 317.7 (81.2)l/min; BDP 319.8 (78.6)l/min) and FEV_1 (FP 1.88 (0.55)l; BDP 1.86 (0.61)l) were also not significantly different.

ADRENAL FUNCTION

The results of the adrenal function studies for all patients are summarised in table 3. Results for 24 hour urinary cortisol levels were only included if no oral steroids had been taken on the day of testing. There were no significant differences in adjusted means for urinary free cortisol levels at eight or 12 weeks, ACTH levels, or baseline and peak serum cortisol levels after LDST between FP and BDP treatment phases. Interestingly, there was a period effect with cortisol levels being generally higher during the second phase of treatment for both sequence groups.

A separate analysis was undertaken for patients who did not receive oral steroids during the treatment phases and is illustrated in table 4. Although the adjusted mean ACTH level was significantly higher during FP treatment (p<0.04), there were no significant differences in urinary free cortisol levels or baseline and peak serum cortisol levels after LDST between the FP and BDP treatment phases.

The low dose synacthen test results suggested the possibility of mild adrenal suppression in both treatment groups, based on previously reported normal data.[12] Mean baseline cortisol levels were below normal (<200 nmol/l) in 15 subjects (55%) given FP and 11 subjects (41%) treated with BDP. Mean LDST stimulated peak serum cortisol levels were below normal (<500 nmol/l) in 18 subjects (67%) treated with FP and 19 subjects (70%) treated with BDP. Separate analysis of patients not receiving oral steroids during the treatment phases did not significantly alter these findings.

GROWTH

There was no evidence of growth suppression during the treatment phases. Mean Ht SDS at baseline was similar for both sequence groups, with the overall group mean being –0.20. There was no significant treatment effect or period effect on growth which remained normal. Mean Ht SDS overall at the end of seven months was –0.22 and both sequence groups grew by a mean of 3.2 cm over this period.

ADVERSE EVENTS

Most of the adverse events were related to exacerbations of asthma or upper respiratory tract infections. Headaches were also common affecting 58.8% of subjects. Most of these adverse events were considered unrelated to inhaled corticosteroids. There was no difference in either the total number of adverse events or the number of adverse events considered possibly related to inhaled corticosteroids between the FP and BDP treatment phases.

Discussion

We have shown that FP 750 µg/day is as effective as BDP 1500 µg/day over 12 week periods in children with persistent severe asthma previously requiring 1000–2000 µg inhaled steroid therapy. Our study confirms the 2:1 efficacy advantage of FP over BDP previously shown in adults on high dose inhaled steroids[9] and extends the similar findings in children on low dose inhaled steroids.[10]

Some of the difficulties involved in conducting a clinical crossover study are highlighted in our findings. Group differences in important background variables such as asthma severity interact with seasonal/periodic effects in the crossover design and make interpretation more difficult. In particular, if subjects tend to be worse during the second treatment period—for

example, winter months—and there is a preponderance of more severe asthmatics in one group, the second treatment period in that group may appear to be disadvantaged. There were significant differences between FP-BDP and BDP-FP sequence groups for sex distribution, frequency of exacerbations, and absolute lung function. The lung function differences were probably related both to difference in height and asthma severity. There was also a significant period effect with more exacerbations occurring in the second 12 week period for both sequence groups. This was most probably related to a seasonal effect as subjects were mainly recruited during summer and thus were in winter during the second treatment phase. Thus, in all our analyses a full covariance model was used and means were adjusted to account for the influence of age, height, sex, seasonal influence, treatment order, and frequency of exacerbations. The potential for a treatment carryover effect existed in the present study. Although we did not have a washout period between treatment periods, averaging symptoms and PEF over the full three month period should have diluted any carryover effect. In addition, a separate analysis comparing only the last month (month 3) of each treatment period was also performed and this showed no difference between FP and BDP treatments. We believe that compliance was adequate as only two subjects (6%) were withdrawn for this reason and the remainder completed all diary cards, clinical appointments, and investigations. We attributed good compliance to monthly clinical reviews with diary card audits and regular telephone liaison by our study nurse.

A potential criticism of our study is that we did not "back titrate" the doses of BDP to ensure that 1500 μg was the minimum effective dose for each patient studied. Our study patients were well known to us and had required high doses of inhaled steroids plus relatively frequent courses of systemic steroids to maintain adequate control of their symptoms. All had been maintained on 1000–2000 μg of inhaled steroids per day for the previous 12 months and two thirds had required 1500–2000 μg per day. We felt that the ethics and logistics of back titration in this patient population would be difficult to implement in our study protocol, especially with treatment periods of only three months on each medication. This decision was supported by the observation that most of the children had significant symptoms and exacerbations during the study periods, with half the patients requiring intervention with systemic steroids. Previous experience in adults using equal doses of BDP and FP has demonstrated an efficacy advantage of FP over BDP.[8] A logical extension of our study would therefore be to compare equal doses of FP and BDP in our study population as an alternative to back titration.

We were unable to demonstrate any differences in urinary free cortisol levels, ACTH levels, and baseline and peak cortisol levels following LDST stimulation between the FP 750 μg and BDP 1500 μg treatment periods. This was unexpected as previous experience in adults had suggested that the 2:1 efficacy advantage of FP over BDP was also associated with significantly less adrenal suppression based on plasma cortisol estimations.[9] A potential confounding factor was the frequent concurrent use of systemic steroids. A separate analysis of children who did not receive systemic steroids during the study period (table 4) did show significantly higher ACTH levels in the FP treatment phase. This suggests that concurrent systemic steroids may have obscured a safety advantage of FP over BDP. However, there were no differences in either urinary free cortisol levels or baseline and peak cortisol levels after LDST. In addition, the relevance of this small difference in ACTH is uncertain, given the high variability of this particular measurement.

It is also possible that systemic or inhaled steroids given prior to the study influenced the adrenal function tests. Unfortunately, we did not have adequate records of the frequency of systemic steroid usage prior to entry. However, given consistent treatment compliance (diary cards, regular telephone contact, and monthly clinic visits) there was an interesting period effect noted—namely, that cortisol measurements were generally higher during the second phase of the study despite the fact that exacerbations (and systemic steroid use) were more frequent during this period. This suggests that pre-study systemic steroid usage influenced the cortisol results, particularly during the first treatment phase. Alternatively, it may reflect an effect of disease activity on adrenal function. Such a rise in plasma cortisol levels has been demonstrated in previous studies both in adults[8 9] and children.[10 17] While prior or concurrent systemic or inhaled steroids could potentially have influenced the adult studies, this was less likely to be a confounding factor in the childhood studies. In particular, the study by Mackenzie *et al*[17] documented that no child had received inhaled or systemic steroids in the six month period preceding the study. It is therefore possible that participation in the study may have improved compliance, and thus asthma control,[18] and this in turn may have influenced adrenal function.

We found that a significant percentage of our study group had evidence of mild adrenal suppression based on the results of LDST. Approximately half the children had baseline morning cortisol levels below normal (<200 nmol/l) while approximately two thirds had peak serum cortisol levels following low dose synacthen stimulation below normal (<500 nmol/l). This contrasts with the study by Broide *et al*[12] which found that 35% of children receiving a mean dose of 500 μg/m^2 BDP or BUD had a peak stimulated cortisol level of <500nmol/l using the LDST. Recent evidence suggests that doses of inhaled steroid as low as 400 μg/day may suppress cortisol production[17] and suppression with higher doses (600–2000 μg) has also been previously demonstrated.[19] The clinical relevance of these degrees of adrenal dysfunction remains uncertain. While it does suggest an effect from the inhaled steroid

therapy, alternative explanations in our study group include concurrent use of systemic steroids, prior use of systemic or inhaled steroids, the effects of the season or the disease itself on the adrenal function. We are unable to distinguish which of these factors was predominant in our patients.[20–22]

Growth was normal in both patient groups. This agrees with previous data suggesting that children with persistent asthma may actually grow better on inhaled steroids.[21 22] No other major adverse effects occurred during the study.

In conclusion, we have shown that FP in a dose of 750 μg/day provides similar efficacy to BDP in a dose of 1500 μg/day in children with persistent severe asthma who previously required high dose inhaled steroids. This confirms the 2:1 potency ratio of FP over BDP in this group of patients. We were unable to demonstrate a safety advantage of FP 750 μg/day over BDP 1500 μg/day in terms of adrenal function. However, measures of adrenal function may have been influenced by concurrent and previous systemic steroid usage and possible effects of disease activity.

We would like to thank Glaxo Wellcome (Australia) for their financial support of the study. Statistical analysis was performed by Bruce Kellett (B & N Kellett, Statistical Consultants, Blackburn South, Victoria, Australia) and we would like to thank him for his thorough analysis and useful comments. Finally, our thanks go to the patients and their parents for participating in the study.

1 Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma. *Am Rev Respir Dis* 1993;**148**:S1–S26.
2 Van Asperen PP, Mellis CM, Sly PD. The role of corticosteroids in the management of childhood asthma. *Med J Aust* 1992;**156**:48–52.
3 Konig P. The risks and benefits of inhaled corticosteroids. *Eur Respir Rev* 1993;**3**:501–10.
4 Russell G. Inhaled corticosteroid therapy in children: an assessment of the potential for side effects. *Thorax* 1994;**49**:1185–8.
5 Isles AF, Robertson CF. Position statement: treatment of asthma in children and adolescents: the need for a different approach. *Med J Aust* 1993;**158**:761–3.
6 Harding SM. The human pharmacology of fluticasone propionate. *Respir Med* 1990;**84**(Suppl A):25–9.
7 Lipworth BJ. New perspective on inhaled drug delivery and systemic bioactivity. *Thorax* 1995;**50**:105–10.
8 Fabbri L, Burge PS, Croonenborgh L, *et al*. Comparison of fluticasone propionate with beclomethasone dipropionate in moderate to severe asthma treated for one year. *Thorax* 1995;**48**:817–23.
9 Barnes NC, Marone G, Di Maria GU, *et al*. A comparison of fluticasone propionate, 1 mg daily with beclomethasone dipropionate 2 mg daily in the treatment of severe asthma. *Eur Respir J* 1993;**6**:877–84.
10 Gustafsson P, Tsanakas J, Gold M, *et al*. 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. *Arch Dis Child* 1993; **69**:206–11.
11 Dickstein G, Shechner C, Nicholson WE, *et al*. Adrenocorticotropin stimulation test; effects of basal cortisol level, time of day, and suggested low dose sensitive test. *J Clin Endocrinol Metab* 1991;**72**:773–8.
12 Broide J, Soferman S, Kivity S, *et al*. Low-dose adrenocortiotropin test reveals impaired adrenal function in patients taking inhaled corticosteroids. *J Clin Endocrinol Metab* 1995;**80**:1243–6.
13 Hammill PVV, Drizid TA, Johnson TL, *et al*. Physical growth: National Centre for Health statistics percentiles. *Am J Clin Nutr* 1979;**32**:607–29.
14 Enright PL, Sherrill DL, Lebowitz MD. Ambulatory monitoring of peak expiratory flow. Reproducibility and quality control. *Chest* 1995;**107**:657–61.
15 Goldstein DE, Konig P. Effect of inhaled beclomethasone dipropionate on hypothalamic-pituitary-adrenal axis functions in children with asthma. *Pediatrics* 1983;**72**:60–4.
16 Gillings D, Koch G. The application of the principle of intention to treat to the analysis of clinical trials. *Drug Inf J* 1991;**25**:411–24.
17 Mackenzie CA, Weinberg EG, Tabachnik E, *et al*. A placebo controlled trial of fluticasone propionate in asthmatic children. *Eur J Pediatr* 1993;**152**:856–60.
18 Reiser J, Warner JO. The value of participating in an asthma trial. *Lancet* 1985;i:206–7.
19 Doull IJM, Donovan SJ, Wood PJ, *et al*. Blood spot cortisol in mild asthma: the effect of inhaled corticosteroids. *Arch Dis Child* 1995;**72**:321–4.
20 Kinan TK, Reid IW, Carter PE, *et al*. Effects of high doses of inhaled corticosteroids on adrenal function in children with severe, persistent asthma. *Thorax* 1993;**48**:599–602.
21 Merkins PJFM, Van Esssen-Zandvliet EEM, Duiverman EJ. Long-term effect of inhaled corticosteroid on growth rate in adolescents with asthma. *Pediatrics* 1993;**91**:1121–6.
22 Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;**88**:373–81.