HPA-axis effects of nebulised fluticasone propionate compared with oral prednisolone in childhood asthma

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Abstract The aim of this study was to compare the effect of 7 days nebulised fluticasone propionate (FP) with oral prednisolone on 24-h urinary-free cortisol excretion, systemic exposure and safety. This was a randomised, double-blind, double-dummy, two-way crossover study. Thirty-one children (19 male, 12 female, mean age 8 years) with stable asthma were randomly assigned to 7 days treatment with either FP Nebules™ (2 × 0.5 mg/2 ml bd) or prednisolone tablets once daily (2 mg/kg/day for 4 days [maximum 40 mg] followed by 1 mg/kg/day or half the original dose for 3 days [maximum 20 mg]). After a 2–4 week washout period, patients received the second treatment for 7 days, followed by a 2-week follow-up visit. The primary outcome measure was 24-h urinary-free cortisol concentrations corrected for creatinine. Nebulised FP (1 mg bd) had significantly less effect on 24-h urinary-free cortisol excretion than oral prednisolone (8.9 ng/ml for FP and 5.0 ng/ml for prednisolone, P=0.001). Systemic exposure to FP was also low. In conclusion, FP Nebules™ had significantly less effect on hypothalamic–pituitary–adrenal axis function than oral prednisolone in asthmatic children when used at doses recommended for the treatment of an acute exacerbation of asthma.

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Keywords fluticasone propionate; Nebules™; prednisolone; asthma; urinary cortisol.

INTRODUCTION

Current international guidelines for the management of acute severe asthma advise treatment with high-dose (usually nebulised) β_2-agonists and a short course of systemic corticosteroids (1). Oral prednisolone (1–2 mg/kg/day) is recommended for children aged 5–15 years by the British Guidelines on Asthma Management (2). However, prednisolone given daily to children, even at low doses (2.5–5.0 mg/day), has a significant adverse effect on short-term linear growth (3) and longer-term statural growth (4). Although hypothalamic–pituitary–adrenal (HPA) axis function rapidly returns to normal after a single short course of prednisolone, markers of bone metabolism can remain abnormal for several weeks (5). Moreover, children who receive more than four courses of systemic corticosteroid in one year, show persistently reduced cortisol responses to Synacthen (6). The optimal dose or duration of systemic corticosteroid treatment for acute asthma is not known, and there is striking inconsistency in the use of systemic corticosteroids to treat acute asthma in children, even between hospitals in the same health region (7).

High-dose inhaled corticosteroid is a potential alternative to oral prednisolone in the treatment of acute asthma attacks in children (8). Large doses of beclomethasone dipropionate (BDP) (9) or budesonide (10) reduced the severity of acute episodic asthma in children, but there was no reduction in hospital admission rate, or requirement for oral corticosteroid. Fluticasone propionate (FP) (1000 μg/day), via metered-dose inhaler (MDI) and spacer device, improved morning and evening peak expiratory flow (PEF) to a greater extent than oral prednisolone (2 mg/kg/day for 4 days followed by 1 mg/kg/day for 3 days) in children presenting with an acute exacerbation of asthma (11).

During an acute exacerbation of asthma lung function is severely compromised, and it is critical that the drug is delivered to the lung in a manner that is independent of patients' inspiratory flow or co-ordination. Inhaled medication may be difficult to administer by powder inhaler

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or MDI when a child is acutely dyspnoeic. The use of a nebulised corticosteroid would allow greater ease and reliability of drug delivery to the lungs. Therefore, a nebulised corticosteroid may be a suitable alternative to oral prednisolone in the treatment of acute asthma in children.

Recently, a nebulised formulation of FP has been developed (12). FP has a favourable therapeutic ratio to those inhaled corticosteroids already in use, due to its high topical activity, high affinity for the glucocorticoid receptor and low oral bioavailability (13). In adults, the estimated systemic bioavailability of nebulised FP is only 8% of the nominal dose, whereas that for budesonide is 13% with nebuliser alone (72% of dose to patient) or 15% with a Spira synchroniser (63% of dose to patient) (14). In children (3–6 years), the systemic bioavailability of nebulised budesonide is approximately half that found in adults (6% of the nominal dose) and 26% of the dose to patient (15).

In a previous large, double-blind, randomised, controlled study in children with an acute exacerbation, nebulised FP (1 mg for 7 days) significantly increased PEF compared with oral prednisolone (16). However, a comparative assessment of the effects of FP and prednisolone on HPA axis function was not possible, due to high cross-reactivity of the cortisol assay with prednisolone. No previous studies have assessed the systemic effects of high-dose nebulised FP in children. In the present study, we have compared the effect of nebulised FP with oral prednisolone on HPA axis function, measured by a sensitive assay of 24-h excretion of urinary-free cortisol in children with chronic stable asthma.

METHODS

Study design

The study had a two-centre, randomised, double-blind, double-dummy, two-way crossover design (Fig. 1). A randomisation code was generated and at visit one investigators allocated treatment numbers in consecutive order, starting with the lowest number available to them. Both the patient and the investigator were blinded to treatment allocation.

Following an initial clinic visit (Visit 1), patients were treated on an out-patient basis and monitored with six home or clinic visits (Visits 2–Visit 7 inclusive) during the 4-week crossover period plus one follow-up visit (Visit 8) (Fig. 1). The protocol was approved by the Investigational Centre Research Ethics Committees and conducted according to Good Clinical Practice guidelines, in accordance with the Declaration of Helsinki. An informed consent form signed by each patient or parent/guardian was obtained before enrolment in the study.

Study population

Patients were eligible to take part in the study if they met the following criteria at screening: were aged 4–16 years inclusive; had a clinical diagnosis of asthma in which all other chronic respiratory diseases had been excluded; were able to use a Sidestream™ nebuliser (Medicaid, U.K.) with parental assistance if required. Inhaled corticosteroids up to 200 μg/day of FP or the equivalent were permitted. Patients were excluded from the study if they had received any systemic corticosteroids or parenteral methylxanthine within 2 weeks of the screening visit, or oral/parenteral corticosteroids for more than 7 days during the 4 weeks before the start of the study; had been admitted to hospital due to respiratory disease within the previous 2 weeks; had a serious uncontrolled disease, or any disease likely to interfere with the objectives of the study.

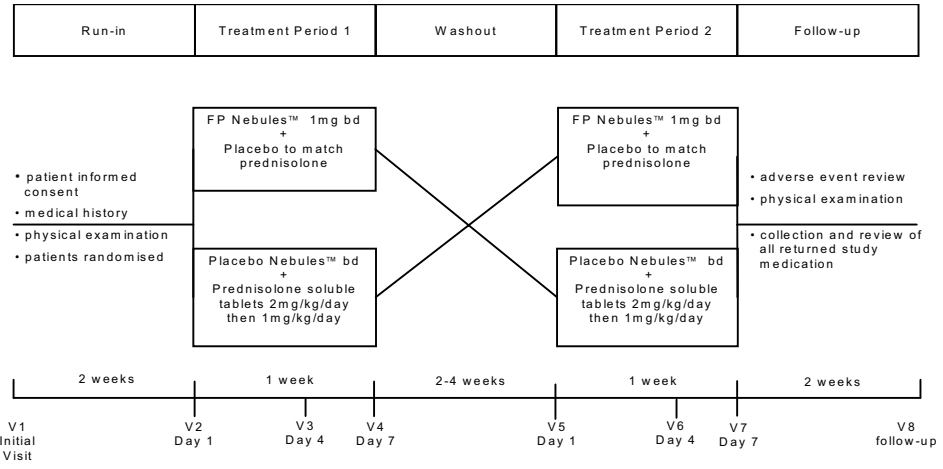

Fig 1. Study design.

Study protocol

Thirty-one patients with stable asthma were enrolled into the study and randomly assigned to one of the following treatment groups for 7 days:

- FP Nebules™ (2 × 0.5 mg/2 ml) bd and placebo to match prednisolone (soluble) tablets once daily.
- Prednisolone tablets once daily: 2 mg/kg/day (maximum 40 mg) for 4 days, followed by 1 mg/kg/day (maximum 20 mg) or half the original dose for 3 days, and placebo to match FP Nebules™ (2 × 0.9% saline/2 ml bd).

There was a washout period 2–4 weeks between treatments. The technique for nebuliser administration was the same as that used in a previous trial of efficacy of FP Nebules (16). Nebulised medication was administered to dryness using a mouthpiece although a mask was permitted if the child was unable or unwilling to use the mouthpiece. Treatment was given twice daily, between 08.00 and 09.00 in the morning, and 17.00 and 19.00 in the evening. Soluble tablets were taken once daily between 08.00 and 09.00 in the morning. Patients continued to take their existing inhaled β_2-agonist on an 'as required' basis for relief of symptoms. After a 2–4 week washout period, subjects received the second treatment for 7 days followed by a 2-week follow-up period.

Safety measures

24-h urinary-free cortisol concentrations. The 24-h urine collection was started and completed before treatment (day 0) and then on day 7 of each treatment period. Urine collection started on the morning of the day before the first dose (first urine on rising was not collected so that all patients started urine collection at the same time), and finished after the first urine sample on rising on treatment day 1 (pre-dose). The second collection of each treatment period started on day 7 (first urine on rising was not collected), and finished after the first urine sample on day 8.

The volume of urine was measured at the clinic and a 20 ml sample was labelled, stored and frozen at -20°C until analysis. Urine samples were prepared by an automated sequential trace enrichment of dialysates system, and separated by reverse-phase high-pressure liquid chromatography (HPLC) with subsequent ultraviolet detection of the resolved analyte (lower limit of quantification = 5 ng/ml). As prednisolone is known to cross-react with cortisol in immunoassay methods of analysis, an HPLC assay method was used in this study, which was validated to ensure that FP and prednisolone did not interfere with the chromatographic detection of cortisol. The reference ranges for urinary-free cortisol excretion per day for our laboratory were 2000–27000 ng/day for subjects aged 4–12 years and 5000–55000 ng/day for subjects aged 13–16 years.

Pharmacokinetic measures. During each treatment period, a single venous blood sample was requested between days 4 and 6 inclusive. Blood sampling was not compulsory. Patients who were unable or unwilling to give a sample could abstain. Each patient was randomised (block size=4) to have blood taken at one of four intervals relative to the morning dose of study medication on days 4–6:

Interval 1: between 1 h and immediately before the morning dose.

Interval 2: between 15 min and 1.5 h after the morning dose.

Interval 3: between 3 and 8 h after the morning dose.

Interval 4: between 9 and 11 h after the morning dose.

Whole blood (4 ml) was drawn into a lithium–heparin collection tube. The contents were mixed thoroughly and centrifuged at 1500g for 10 min at 4°C within 2–3 hours of collection. Plasma was separated, frozen and stored at -20°C until analysis. Plasma samples were analysed in duplicate for FP using solid-phase extraction in combination with liquid chromatography tandem mass spectrometry (LC-MS). Plasma samples were analysed in duplicate for prednisolone using solid phase extraction in combination with liquid chromatography and ultraviolet detection. The method has been validated with a lower limit of quantification of 20 ng/ml.

Adverse events. An adverse event was defined as any untoward medical occurrence experienced by a patient and rated as mild, moderate or severe. All adverse events were documented.

Statistical analyses

The primary endpoint of this study was 24 h urinary-free cortisol concentrations adjusted for creatinine (urinary-free cortisol concentration/creatinine concentration ng/mg). A value of 0.55 was estimated as the residual standard deviation for log-transformed values of urinary-free cortisol concentrations corrected for creatinine. Power calculations indicated that data from 26 evaluable volunteers were required to detect a 35% difference in the FP/prednisolone ratio of urinary-free cortisol concentration:creatinine concentrations at the end of treatment, at a 5% significance level, with 80% power.

Values of urinary-free cortisol corrected for creatinine were log-transformed and analysed using an analysis of covariance, allowing for effects due to subject, period, baseline and treatment. However, a large proportion of the urinary-free cortisol values (prior to correction for creatinine) were below the lower limit of quantification (BLLQ) of 5 ng/ml (15% of day 1 values and 58% of day 8 values). The post-treatment values BLLQ were likely to be due to a treatment effect, so to include them in the

analysis, a value of 2.5 ng/ml was assigned to pre- and post-treatment BLLQ values (mid-point of the 0–5 ng/ml range BLLQ). However, to aid interpretation, the analysis was repeated assigning low (1.50 ng/ml) and high (4.50 ng/ml) values.

It was recognised that missing pharmacokinetic data could arise due to the inclusion of young children in the study who may have been unwilling to provide a blood sample, and also that many samples may have contained FP or prednisolone concentrations BLLQ of the assay. Pharmacokinetic parameters could not be calculated as only two FP samples were above the assay limit of 20 pg/ml. An estimate was made of area under curve (AUC_{0-24}) and maximum observed plasma concentration (C_{max}). The true C_{max} could not be calculated as patients were sampled at different times.

RESULTS

Number of patients randomised to treatment

Thirty-one patients were randomised to treatment, 16 patients to the FP/prednisolone sequence group and 15 patients to the prednisolone/FP sequence group. There was no significant difference in baseline characteristics between the two treatment groups (Table 1).

24-h urinary-free cortisol concentrations

The pre- and post-dose urinary-free cortisol concentrations are presented in Fig. 2. Four of 29 (14%) and 5 of 31 (16%) patients had a BLLQ cortisol concentration on day 0 before taking FP or prednisolone, respectively. Day 0 urinary cortisol concentrations for patients receiving FP or prednisolone did not differ significantly in either treatment sequence, suggesting that the washout periods were long enough. However, post-treatment, only 8 of 28 (29%) patients taking FP compared with 25 of 29 (86%) patients taking prednisolone had a BLLQ cortisol concentration. Of the eight patients taking FP who had a BLLQ cortisol concentration post-treatment, three also recorded BLLQ values pre-treatment. Of the 25 patients taking prednisolone with BLLQ values post-treatment, only four recorded BLLQ values pre-treatment. Hence, of the subjects with quantifiable values pre-treatment, 5/25 (20%) patients had BLLQ values after treatment with FP compared with 21/26 (81%) patients after treatment with prednisolone. There is a clear difference between the treatments in the effect on urinary-free cortisol, with approximately three times as many subjects having unquantifiable cortisol concentrations after treatment with prednisolone compared with FP.

In the 4–12 year age band, one subject had cortisol <2000 ng/day on Day 8 following FP and one on Day 8 following prednisolone; one subject had baseline cortisol >27000 ng/day and <2000 ng/day on Day 8 following FP; one subject had baseline (Day1) cortisol <2000 ng/day for both treatment periods. In the 13–16 year age band, one subject had baseline and Day 8 cortisol <5000 ng/day following prednisolone.

A summary of urinary-free cortisol adjusted for creatinine is given in Table 2. For the purpose of analysis, a value of 2.5 ng/ml was given to all values BLLQ. Nebulised FP had significantly less effect on 24-h urinary-free cortisol excretion compared with oral prednisolone (P=0.001). Prednisolone-reduced urinary-free cortisol concentrations by 61% compared with 34% in the FP group. An estimate of the ratio of treatment difference (FP/prednisolone) with associated 95% confidence interval was 1.8 [1.3, 2.5]. There was an estimated 80% larger reduction in cortisol levels after treatment with

Table 1. Characteristics of patients at baseline

Patient characteristics	FP/prednisolone sequence (n=16)	Prednisolone/FP sequence (n=15)
Sex	10 male/6 female	9 male/6 female
Age (years)	8.7 ± 2.7	7.7 ± 2.6
Height (cm)	131.3 ± 16.3	126.9 ± 14.9
Weight (kg)	30.8 ± 12.3	30.3 ± 12.8
No. of patients on corticosteroids at randomization	12 (75%)	10 (67%)
Beclomethasone dipropionate	5 (31%)	6 (40%)
Budesonide	7 (44%)	2 (13%)
Fluticasone propionate	0	2 (13%)
Median (range) pre-study corticosteroid dose (μg bd)		
Beclomethasone dipropionate	200 (50–200)	150 (100–200)
Budesonide	200 (50–200)	200 (200–200)
Fluticasone propionate	—	100 (100–100)

Results are expressed as the mean ± SD unless otherwise stated.

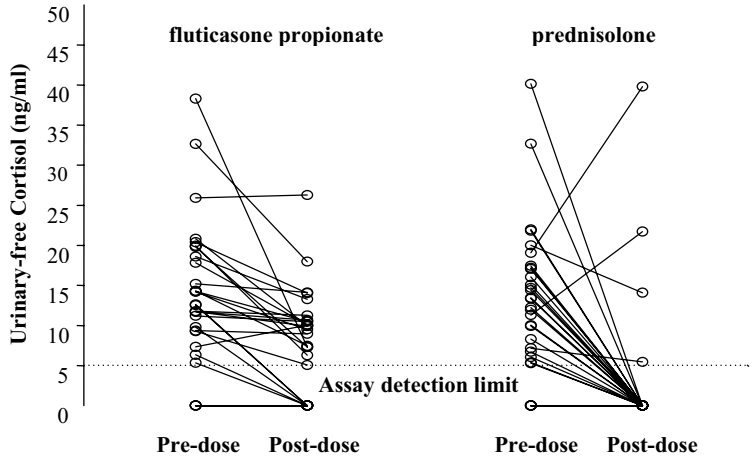

Fig. 2. Twenty-four hour urinary-free cortisol in children after 7 days dosing with nebulised fluticasone propionate (1 mg bd; *n*=28) or oral prednisolone (1–2mg/kg/day; n=29). Four patients in the FP group and five patients in the prednisolone group had 24-h urinary-free cortisol concentrations below the lower limit of quantification pre-dose (represented by single dots beneath the dotted line of the assay detection limit).

Table 2. Effect of treatment with nebulised fluticasone propionate (1 mg bd) or oral prednisolone (1–2 mg/kg/day) for 7 days on urinary-free cortisol:creatinine ratio (ng:mg)

	Urinary-free cortisol: creatinine ratio (ng:mg) FP group (*n*=28)	Urinary-free cortisol: creatinine ratio (ng:mg) Prednisolone group (*n*=29)
Day 1 (pre-treatment)	14.0	12.8
Day 8 (7 days post-treatment)	9.2	5.0
Adjusted mean	8.9*	5.0

Assuming all values below the lower limit of detection=2.5 ng/ml.
Adjusted mean: mean after taking account of covariates which were included in the statistical analysis (e.g. age, sex, centre/country).
*P=0.001 compared with oral prednisolone.

prednisolone compared with FP with no evidence of carry-over in the analysis (P=0.492). Additional analyses were also performed using BLLQ values that were assumed to be low (1.5 ng/ml) and high (4.5 ng/ml). When values BLLQ were assumed to be 1.5 ng/ml, a highly significant difference was observed between treatments ($P < 0.0001$). However, even when all values below BLLQ were assumed to be 4.5 ng/ml, a significant difference between treatments was still seen (P=0.044), with an estimate of the ratio of treatment difference reduced to 1.3.

Plasma concentrations of fluticasone propionate and prednisolone

Twenty-one patients provided blood samples (10 FP; 11 prednisolone). Fig 3 summarises the observed plasma concentrations of prednisolone and FP. The observed FP data were sparse, with an observed C_{max} of 21 pg/ml and an AUC_{0-24} of 72.7 pgh/ml. The observed daily systemic exposure to prednisolone was observed C_{max} 811.5 ng/ml and AUC_{0-24} of 2179.2 ng h/ml.

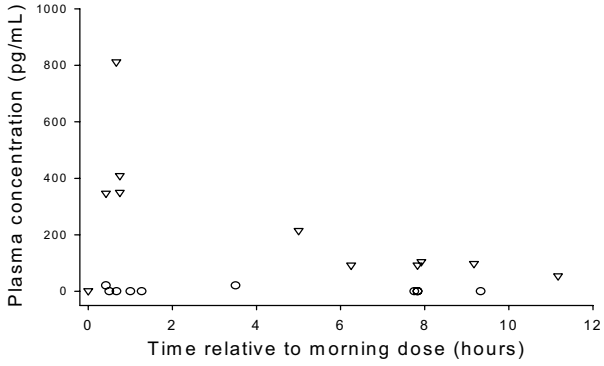

Fig. 3. Plasma concentration–time profiles for fluticasone propionate (○ *n*=2) and prednisolone (▽ *n*=11) at steady state generated by blood sampling in children.

Adverse events

Both treatments were well-tolerated, with no significant difference in the number of patients who experienced an adverse event during treatment (*n*=8 FP group; *n*=7 pre-

dnisolone group). Three (10%) patients experienced a drug-related adverse event (assessed by the investigator) during treatment with FP compared with four (13%) patients during treatment with prednisolone. The drug-related adverse events were cough (n=2 FP group; n=1 prednisolone group), throat irritation (n=2 prednisolone group), candidiasis of the mouth/throat (n=1 prednisolone group) and dizziness (n=1 FP group). No serious adverse events were reported during the study.

DISCUSSION

This study showed that 7 days treatment with nebulised FP (1 mg bd) had significantly less effect on 24-h urinary-free cortisol excretion than oral prednisolone (2 mg/kg/day for 4 days then 1 mg/kg/day for 3 days) in children with chronic stable asthma. FP reduced the 24-h urinary-free cortisol concentration by 34%, compared with 61% in the prednisolone group (assuming values BLLQ = 2.5 ng/ml).

Inhaled corticosteroids have fewer systemic side-effects than oral or parenteral corticosteroids. In children suffering from a severe asthmatic exacerbation, high-dose inhaled budesonide (1600 μg/day) via Turbuhaler did not significantly reduce serum cortisol concentrations after 1 week of treatment. However, serum cortisol concentrations were significantly decreased in almost all of the children who received oral prednisolone (2 μg/kg/day), at both 0800 hours and 1 h after Synacthen stimulation(8). Similarly, in children with moderate bronchial asthma, inhaled FP (200 μg/day) or budesonide (800 μg/day) for $\geq$ 4 weeks had no effect on HPA axis function, but children who received oral prednisolone showed a marked reduction of 24-h plasma cortisol concentration and a significantly reduced response to human corticotropin releasing hormone (17).

In the present study, four patients in the FP group (14% period 1 and 2) had urinary-free cortisol concentrations that were BLLQ prior to study treatment on day 1 compared with five patients (16% period 1 and 2) in the prednisolone group. Each of the four patients with cortisol concentrations BLLQ in the FP group were on inhaled corticosteroids at randomisation (n=1 FP 100 μg bd; n=1 budesonide 200 μg bd; n=2 BDP 100 μg bd), compared with two of the five patients in the prednisolone group (n=2 BDP 100 μg bd). A carry-over effect of nebulised FP from the first period could potentially explain the BLLQ urinary cortisol concentrations in the remaining three patients in the prednisolone group. However, looking at period 1 data only to eliminate any carry-over effect, two out of four patients in the prednisolone group who had urinary cortisol concentrations BLLQ prior to study treatment on day one were not on inhaled corticosteroids at randomisation. The low 24-h urinary cortisol concentrations in these patients, may have been due to previous use of inhaled or oral corticosteroids before enrolment in the study. On the other hand, for cortisol to appear in the urine cortisol binding globulin in the circulation must be saturated. This requires serum concentrations of at least 400 nmol/l. It is therefore possible for urine-free cortisol to be very low without adrenal suppression and perhaps not surprising that some of the pre-treatment values were low. It is also reasonable to assume that the endogenous corticosteroid production in these children, who were stable and well, would be lower than in asthmatic children during an exacerbation. There was however a striking difference in the number of children with cortisol levels below the limit of sensitivity of the assay post-treatment with oral prednisolone compared with post-treatment with nebulised fluticasone. The response of the adrenal gland to human corticotrophin releasing hormone was not assessed in this study, so we do not know precisely the clinical relevance of our observations. Nevertheless, our results strongly suggest that the potential for clinically important adrenal suppression is much greater after treatment with prednisolone than after treatment with nebulised fluticasone.

The present study was not powered for within group statistical analysis, but transient effects of FP on HPA axis function are not unexpected, as they are seen with all inhaled corticosteroids at the higher end of the recommended dose range. In adults, the systemic bioavailability of FP is approximately two-fold less in patients with asthma than in healthy volunteers (13,18,19). Patients with an acute exacerbation of asthma, therefore, may have less systemic absorption of nebulised FP than was observed in the present study in patients with less severe asthma.

The secondary objective of this study was to examine the systemic exposure to both treatments using limited blood sampling at a point of steady-state and population pharmacokinetics. However, only two FP samples were above the assay limit of 20 pg/ml which most likely reflects the fact that FP is cleared very rapidly from the systemic circulation by metabolism to an inactive carboxylic metabolite by the cytochrome P450 isoenzyme CYP3A4 (20).

Previously published studies have demonstrated the efficacy of nebulised corticosteroids in the treatment of acute asthma in children. Manjra and colleagues (16) showed that nebulised FP (1 mg for 7 days) significantly increased PEF compared with oral prednisolone in children experiencing an acute exacerbation of asthma. Nebulised budesonide also increased the rate of recovery of children presenting with an acute exacerbation of asthma compared with oral prednisolone (21,22). These studies confirm the efficacy of nebulised corticosteroids versus oral prednisolone in children with an acute exacerbation of asthma, and combined with the superior safety profile of FP demonstrated in the present study, supports an overall better therapeutic ratio for nebu-

lised FP. The results of the present study demonstrate that, in children with chronic stable asthma, treatment with nebulised FP (1 mg bd for 7 days) had significantly less effect on 24-h urinary-free cortisol excretion than oral prednisolone. At these doses, FP has previously been shown to be more effective than oral prednisolone in the management of acute exacerbations of asthma in children (16). In conclusion, FP Nebules™ had less effect on HPA axis function than oral prednisolone in asthmatic children when used at doses recommended for the treatment of an acute exacerbation of asthma.

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REFERENCES

1. Global Initiative for Asthma. Global strategy for asthma management and prevention. NHLBI/WHO workshop report March 1993. Bethesda: National Institutes of Health, National Heart, Lung and Blood Institute. Publication number 96-3659B. Revised November 1998.
2. British Thoracic Society. Guidelines on the management of asthma. *Thorax* 1997; **52:** S1–S21.
3. Wolthers OD, Pedersen S. Short term linear growth in asthmatic children during treatment with prednisolone. *BMJ* 1990; **301:** 145–148.
4. Efthimiou J, Barnes P. Effect of inhaled corticosteroids on bones and growth. *Eur Respir J* 1998; **11:** 1167–1177.
5. Zora JA, Zimmerman D, Carey TL, O'Connell EJ, Yunginger JW. Hypothalamic–pituitary–adrenal axis suppression after short-term, high-dose glucocorticoid therapy in children with asthma. *J Allergy Clin Immunol* 1986; **77:** 9–13.
6. Dolan LM, Kesarwala HH, Holroyde JC, Fischer TJ. Short-term, high-dose, systemic steroids in children with asthma: the effect on the hypothalamic–pituitary–adrenal axis. *J Allergy Clin Immunol* 1987; **80:** 81–87.
7. Anderson HR. Trends and district variations in the hospital care of childhood asthma: results of a regional study 1970–85. Thorax 1990; **45:** 431–437.
8. Volovitz B, Bentur L, Finkelstein Y, *et al*. Effectiveness and safety of inhaled corticosteroids in controlling acute asthma attacks in children who were treated in the emergency department: a controlled comparative study with oral prednisolone. *J Allergy Clin Immunol* 1998; **102:** 605–609.
9. Wilson NM, Silverman M. Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home. *Arch Dis Child* 1990; **65:** 407–410.
10. Connett G, Lenney W. Prevention of viral induced asthma attacks using inhaled budesonide. *Arch Dis Child* 1993; **68:** 85–87.
11. Verona E, Ahel V, Williams L, Medley HV. A multicentre, randomised, double-blind, double-dummy, parallel group study comparing efficacy and safety of fluticasone propionate (FP) 500 μg bid delivered by metered dose inhaler (MDI) and spacer device with oral prednisolone. *Am J Respir Crit Care Med* 1998; **157:** A711.
12. Westbroek J, Saarelainen S, Laher M, O'Brien J, Barnacle H, Efthimiou J. Oral steroid sparing effect of two doses of nebulized fluticasone propionate and placebo in patients with severe chronic asthma. *Respir Med* 1999; **93:** 689–699.
13. Falcoz C, Mackie AE, McDowall J, *et al*. Oral bioavailability of fluticasone propionate in healthy subjects. *Br J Clin Pharmacol* 1996; **41:** 459–460.
14. Dahlstrom K, Larsson P. Lung deposition and systemic availability of budesonide inhaled as nebulised suspension from different nebulisers. *J Aerosol Med* 1995; **8:** 79.
15. Agertoft L, Andersen A, Weibull E, Pedersen S. Systemic availability and pharmacokinetics of nebulised budesonide in preschool children. *Arch Dis Child* 1999; **80:** 241–247.
16. Manjra AL, Price J, Lenney W, Hughes S, Barnacle H. Efficacy of nebulised fluticasone propionate compared with oral prednisolone in children with an acute exacerbation of asthma. *Respir Med* 2000; **94:** 1206–1214.
17. Hoffmann-Streb A, L'Allemand D, Niggemann B, Buttner P, Wahn U. Adrenal cortex function in children with bronchial asthma in fluticasone therapy. *Monatsschr Kinderheilk* 1993; **141:** 508–512.
18. Brutsche MH, Carlan Brutsche I, Munavvar M, *et al*. Pharmacokinetics and systemic effects of inhaled fluticasone propionate (FP) are different in asthmatics (A) and normal volunteers (N). *Eur Respir J* 1999; **14:** 345s.
19. Hallett C. Corticosteroid treatment of asthma: now at the crossroads. *Respir Med* 1999; **93:** 292–294.
20. Harding SM. The human pharmacology of fluticasone propionate. *Respir Med* 1990; **84 (**Suppl A): 25–29.
21. Devidayal, Singhi S, Kumar L, Jayshree M. Efficacy of nebulized budesonide compared to oral prednisolone in acute bronchial asthma. *Acta Paediatr* 1999; **88:** 835–840.
22. Daugbjerg P, Brenoe E, Forchhammer H, *et al*. A comparison between nebulized terbutaline, nebulized corticosteroid and systemic corticosteroid for acute wheezing in children up to 18 months of age. *Acta Paediatr* 1993; **82:** 547–551.