Estimation of the dose of fluticasone propionate inhaled by infants after bronchiolitis: Effect on urinary cortisol excretion

Jackson Wong, MRCP(UK), MRCPCH,[a] Tim Davies, PhD,[b] and Christopher O'Callaghan, FRCP, FRCPCH, DM, PhD *Leicester, United Kingdom*

Background: Information on the dose of steroid infants inhale from spacer devices and its potential effect on adrenal suppression is limited.
Objective: We sought to determine the total dose of fluticasone propionate (FP) inhaled from a spacer device (Babyhaler) with face mask attachment by infants recovering from acute bronchiolitis and the effect of inhaled FP on the infants' overnight urinary cortisol/creatinine ratios (UCCRs).
Methods: Infants studied were recovering from acute bronchiolitis. In study 1, 22 infants inhaled 150 μg of FP through the Babyhaler. The likely inhaled dose was estimated by trapping it on a filter held within the face mask. In study 2, 40 infants had UCCRs measured before and during 3 months of treatment with either FP (150 μg twice daily, n = 20) or placebo (n = 20).
Results: In study 1 the mean ± SD dose of captured FP was 12.8 ± 6.9 μg (ie, 2.1 ± 1.2 μg/kg). In study 2 the pretreatment UCCR medians (interquartile ranges) were as follows: FP, 22.8 (23.0) nmol/mmol; placebo, 24.0 (28.3) nmol/mmol. Within-group UCCR changes (median and interquartile range ΔUCCR) were significantly different in the FP group (–8.9 and –20.6 nmol/mmol at 6 weeks and –12.6 and –25.9 nmol/mmol at 12 weeks, respectively; *P* = .0008) but not in the placebo group (–5.8 and –10.7 nmol/mmol at 6 weeks and +0.3 and –17.9 nmol/mmol at 12 weeks, respectively; *P* = .45). Inter-group changes were insignificant in the follow-up period (6 weeks, *P* = .52; 12 weeks, *P* = .19).
Conclusion: After bronchiolitis, infants are likely to inhale approximately 8% of the nominal steroid dose from the Babyhaler. UCCRs can be used to monitor the bioavailability of inhaled steroids in young infants. (J Allergy Clin Immunol 2002;110:721-7.)

Key words: *Inhaled steroid, aerosol, Babyhaler, spacer device, aerosol drug delivery, urinary cortisol creatinine ratio, bronchiolitis, infant*

Abbreviations used
FP: Fluticasone propionate
IQR: Interquartile range
MDI: Metered-dose inhaler
UCCR: Urinary cortisol/creatinine ratio

Recently, we reported the results of a double-blind, randomized, placebo-controlled trial[1] that was designed to determine whether infants receiving an inhaled steroid, fluticasone propionate (FP), for 3 months had less postbronchiolitic respiratory symptoms than infants receiving placebo. The trial did not find the use of inhaled steroids to be efficacious in these patients over a range of parameters, including symptom reduction, use of rescue medications, overnight oxygen saturation, overnight cough scores, and infant lung function.

The absence of beneficial effects might either reflect an intrinsic ineffectiveness of this treatment or inadequate delivery of inhaled steroids. The possibility that steroid therapy is ineffective is supported by negative trials with oral[2] or nebulized[3] corticosteroids in infants of similar age, although end points used in these studies were slightly different than ours.[1] However, studies also exist that suggest inhaled steroids could reduce postbronchiolitic respiratory symptoms.[4-6] Therefore it was essential to determine that the delivery of inhaled steroids was adequate in our study. We investigated the dose delivery of inhaled steroids to infants recovering from acute bronchiolitis as part of a clinical trial.[1] We estimated the total dose of corticosteroids inhaled through a spacer device used by infants with bronchiolitis and used urinary cortisol levels as a marker of the systemic bioavailability of the inhaled corticosteroid.[7,8]

METHODS

Patients

Infants requiring hospital admission because of acute viral bronchiolitis were recruited immediately before hospital discharge. Acute bronchiolitis was diagnosed by using the criteria suggested by Court[9]: infants presented with a clinical syndrome characterized by coryzal phase, dry repetitive cough, difficulty in breathing, rapid respiratory rate, chest distension, chest in-drawing, fine inspiratory crepitations, expiratory wheeze, nasal discharge, and fever during a bronchiolitis season. Exclusion criteria were as follows: children born before 36 weeks' gestation and those older than 12 months,

From [a]the Department of Child Health and Institute of Lung Health and [b]the Department of Chemical Pathology, University of Leicester, Clinical Sciences Building, Leicester Royal Infirmary, Leicester.
Supported by Glaxo-Wellcome.
Received for publication January 9, 2002; revised July 30, 2002; accepted for publication August 8, 2002.
Reprint requests: Christopher O'Callaghan, Department of Child Health and Institute of Lung Health, University of Leicester, Clinical Sciences Building, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX, United Kingdom.

0091-6749/2002 $35.00 + 0 **1/81/128858**
doi:10.1067/mai.2002.128858

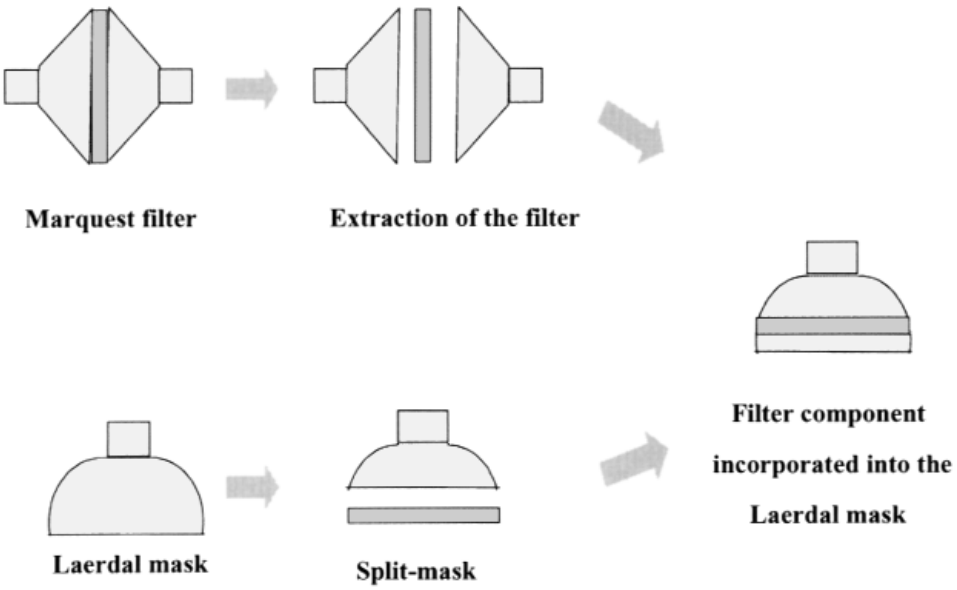

FIG 1. The filter component of the Marquest filter was removed and glued between the split Laerdal face mask. Minimal dead space was achieved.

infants with congenital heart disease or syndromic abnormalities, and infants with a history of artificial ventilatory support or chronic illnesses. Written informed consent was obtained, and the age and weight of the infants were recorded.

Two studies were conducted. In study 1 (dose-estimate study) 22 previously healthy infants were hospitalized with a diagnosis of bronchiolitis. In study 2 (urinary steroid study) 48 infants with bronchiolitis were given 3 months of inhaled FP or placebo through a Babyhaler device as part of a double-blind, randomized, placebo-controlled study.[1]

Study 1: Estimation of inhaled steroids

FP (Flixotide, Glaxo-Wellcome) metered-dose inhalers (MDIs) containing chlorofluorocarbon propellant were used. The total dose of FP inhaled was estimated by capturing the inhaled drug on a filter inserted into the face mask of the Babyhaler spacer device (Glaxo-Wellcome). The silicon Laerdal face mask (Glaxo-Wellcome) from the spacer was cut in half with a rotating cutter (Fig 1). A low-resistance Marquest filter (Respirgard II-Marquest Medical Products) was removed from its case, leaving as little of the filter holding frame as possible. The extracted filter was inserted and glued in between the split face mask by using a thin layer of silicon glue. This design introduced virtually no additional dead space into the face mask. Two reassembled face mask–filter units were subjected to washing and HPLC assay for FP to demonstrate that this procedure did not interfere with the FP HPLC assay.

The following experiment was performed to ensure the filter completely captured the aerosolized FP. An MDI of FP (50 μg per actuation) was shaken for 10 seconds and was then actuated into the spacer 10 times. During this time, air was continually sucked at 60 L/min from the spacer device through the filter inserted in the face mask. The air sucked from the spacer passed through a trap containing 20 mL of methanol, in which FP is soluble. The filter was then removed from the face mask, immersed in methanol containing internal standard, and ultrasonicated for 3 minutes. Tubing distal to the filter was washed, and the total amount of FP from the tubing and the methanol trap was determined by using HPLC.

We have observed that actuation of an MDI into some spacer devices results in the valve opening toward the patient, with escape of part of the aerosol cloud. Because of this shoot-through phenomenon, the following study was conducted to determine the amount of FP that might have impacted on the filter. Three shots of FP (50 μg per actuation) were actuated individually into the spacer. The face mask attached to the spacer had a filter inserted, as described above. The filter was removed, and the amount of FP on it was assayed by means of HPLC. This procedure was repeated on 5 occasions.

HPLC determination of FP

The amount of FP was determined by means of HPLC. Standard solutions of known concentrations of FP (reference substance from Glaxo) were used as reference. HPLC analysis was performed by using a Waters Spherisorb ODS1 column (10 cm × 4.6 mm internal diameter). The mobile phase consisted of a mixture of methanol/0.1% ammonium acetate solution (75:25 vol/vol) with a flow rate of 1.7 mL/min. The injection volume was 100 μL, and triplicate injections were made for each sample and standard. Detection was by UV absorbance at 239 nm. Measurement was by integration of peak area and relationship with an internal standard of benzyl biphenyl. Recalibrations were made throughout the sequence of samples to take account of any changes in the chromatographic conditions.

Clinical study outline

Infants in study 1 were studied before hospital discharge when they were tolerating feeding and no longer required oxygen therapy. Seven of these infants who were breathing quietly and who tolerated the face mask underwent measurements of their tidal volume. An infant pneumotachograph was attached to a face mask to measure the inspiratory and expiratory flow. The pneumotachograph was calibrated immediately before the test by injecting a known volume of air to simulate tidal breathing. When the infant appeared settled, the face mask was applied over the nostrils and mouth, creating a seal with the infant's face for approximately 20 seconds. Tidal volumes were obtained by means of integration of the flow against time with a signal analysis program (Anadat).

TABLE I. Filter deposition of FP aerosol from 22 infants recovering from acute bronchiolitis

Filter deposition of FP (μg of FP or % nominal dose of 150 μg of FP)	Group		
	No. of infants	Mean ± SD	Range
Filter deposition of 150 μg of FP	22	12.7 ± 6.9	2.1-28.4
Percentage of nominal FP dose	22	8.5 ± 4.6	1.4-18.9
Filter deposition of FP in crying infants	18	14.5 ± 6.2	5.7-28.4
Percentage of nominal FP dose in crying infants	18	9.7 ± 4.1	3.8-18.9
Filter deposition of FP in quietly breathing infants	7	8.4 ± 7.0	2.1-21.9
Percentage of nominal FP dose in quietly breathing infants	7	5.6 ± 4.7	1.4-14.6
Filter deposition of FP/kg body weight	22	2.2 ± 1.2	0.5-5.0
Filter deposition of FP/kg in crying infants	18	2.4 ± 1.1	0.6-5.0
Filter deposition of FP/kg in quietly breathing infants	7	1.5 ± 1.1	0.5-3.4

Three infants were tested during both quiet breathing and crying.

All spacers were washed with domestic detergent on the night before the test and allowed to drip dry in air without rinsing in clear water. On the day of the study, 6 shots of FP were fired into the spacer (50 μg per shot) without subsequent inhalation in an attempt to reduce any accumulation of static charge that might have occurred overnight. Parents were taught to use the spacer device and to apply the face mask to their baby's face efficiently. Immediately before using the inhalers, a clean face mask–filter unit was attached to the FP-coated spacer. The face mask was positioned to cover the infant's nostrils and mouth, forming a seal with the infant's face. The MDI was shaken for 5 seconds and actuated, and the parents were instructed to allow the child to breathe from the spacer device for approximately 10 seconds. Two further doses of FP were administered in the same manner. The investigator noted the technique of parents and recorded any observed leaks between the face mask and the infant's face. The filter was removed from the face mask, and the amount of FP was determined by means of HPLC.

The effect of crying and quiet breathing on the amount of FP deposited on the filter was examined. Three infants had multiple tests, and they were represented in both the crying and noncrying groups. If an infant had more than one recording in each category, mean values were calculated for formulation of a group mean.

Effect of inhaled FP on urinary cortisol excretion

Infants in study 2 were randomized to receive either 3 actuations of FP (50 μg per actuation) or placebo twice daily administered through the spacer for 3 months. Overnight urine samples were collected before treatment and again after 6 and 12 weeks for measurement of free cortisol/creatinine ratios. A urine bag was applied to the infant's perineum, and urine was drained overnight into a bottle. Infants given prophylactic inhaled or oral corticosteroid therapy by their doctor were disqualified from the trial. Urinary free cortisol levels were determined by using the Coat-A-Count cortisol RIA test (Diagnostic Products Corporation). This test is a solid-phase RIA whereby iodine 125–labeled cortisol competes for antibody sites over a fixed time with cortisol from the patient's urine sample. To investigate whether age at recruitment could have influenced the urinary cortisol/creatinine ratio (UCCR), we made intergroup comparisons of UCCRs in those younger than and older than 3 months of age.

Ethics approval

The local Leicestershire Ethics Committee approved the studies.

Statistical methods

Because overnight UCCR values were not normally distributed in the placebo group, medians and interquartile ranges (IQRs) between the first- and third-quartile UCCR values were reported. Changes from baseline in overnight UCCRs during the trial treatment period were assessed within and between treatment groups by using the Kruskal-Wallis 1-way ANOVA test and the Wilcoxon test, respectively.

RESULTS

No FP was found in unexposed filters, and no FP escaped through the filter. Actuation of the MDI into the spacer without an infant breathing resulted in a variable amount of FP aerosol passing through the valve and impacting on the filter. The amount of FP (50 μg per actuation) captured on the filter for the 5 experiments was 0, 0.8, 0.3, 0.7, and 0.3 μg per 50-μg actuation (mean ± SD, 0.4 ± 0.29 μg).

Study 1

Twenty-two infants with a mean ± SD age of 4.25 ± 3.3 months (range, 0.5-11 months) and a mean ± SD body weight of 6.1 ± 2.0 kg (range, 3.1-9.9 kg) took part in the study. Thirteen recordings of tidal volume measurements were obtained from 6 infants while they were breathing quietly. Mean values were calculated for each individual where repeated measures of tidal volume were taken from the same infant. The group mean ± SD tidal volume was 5.9 ± 1.1 mL/kg, and the mean ± SD minute ventilation was 259 ± 47.4 mL/kg.

All 22 infants in study 1 were given 3 actuations of 50 μg of FP while breathing through the spacer. Seven of the 22 infants were tested on more than one occasion for collection of FP on the face mask filter, and hence a total of 32 tests were performed. The mean values of the filtered FP from each of these 7 infants were used for the final calculation of group mean values of captured FP from the 22 infants (Table I). The final group mean ± SD was 12.7 ± 6.9 μg per 150 μg of FP actuated. This represented 8.5% of the nominal dose and equated to a mean ± SD dose of 2.2 ± 1.2 μg of FP per kilogram of body weight.

Of the 22 infants, 3 were tested while crying and during quiet breathing. Mean values of each infant were used according to their breathing status for final group mean analysis. A total of 23 studies were performed on 18 crying infants, and 9 studies were performed on 7 quietly

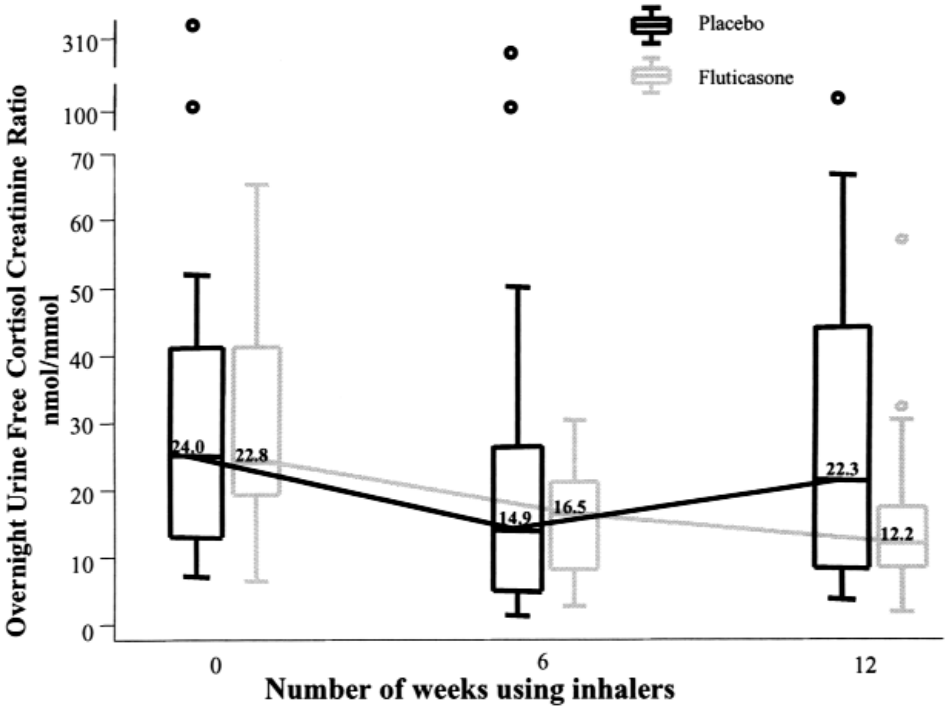

FIG 2. Longitudinal overnight urinary free cortisol profile in FP and placebo groups in infants before and after use of inhalers for 6 and 12 weeks. *Box plots* represent median and first and third quartiles. *Bars* represent upper and lower fences, and *circles* represent outlier values.

breathing infants. In crying infants the group mean ± SD value of captured FP was 14.5 ± 6.2 μg. This was almost twice as much as that for quietly breathing infants (ie, 8.4 ± 7.0 μg). Two quietly breathing infants were tested twice and had no FP recovered on one of the 2 occasions.

Study 2

Forty-eight infants were recruited. Collection of baseline (pretreatment) and subsequent (weeks 6 and 12) overnight urine samples were possible in 40 infants, 20 in each treatment group. Infants in the FP group had a mean ± SD age of 3.8 ± 2.3 months (range, 0.9-10.1 months) and a mean ± SD body weight of 6.4 ± 1.8 kg (range, 2.6-9.7 kg). Those in the placebo group had a mean ± SD age of 3.9 ± 2.4 months (range, 1.4-11.0 months) and a mean ± SD body weight of 6.6 ± 1.8 kg (range, 4.3-10.5 kg). Before commencement of inhaled trial therapy, median and first and third quartiles of overnight UCCRs (in nanomoles per millimoles) were similar between treatment groups (Fig 2).

In the placebo group UCCR values, given as medians, IQRs, and first and third quartiles, were not significantly different from baseline values (24.0, 28.3, 12.0, and 40.3 nmol/mmol, respectively), 6-week values (14.9, 21.3, 5.8, and 27.1 nmol/mmol, respectively; $P = .09$), and 12-week values (22.3, 35.7, 9.3, and 45.0 nmol/mmol, respectively; $P = .94$). Group medians, IQRs, and first and third quartiles for ΔUCCR from baseline levels were also insignificant at 6 weeks (–5.8, –10.7, +12.0, and –22.7 nmol/mmol, respectively) and 12 weeks (+0.3, –17.9, +10.4, and –28.3 nmol/mmol, respectively; $P = .45$).

In the FP group there was a significant reduction in UCCRs, given as medians, IQRs, and first and third quartiles, at baseline (22.8, 23.0, 18.2, and 41.2 nmol/mmol, respectively), 6 weeks (16.5, 13.1, 8.3, and 21.3 nmol/mmol respectively; $P = .007$), and 12 weeks (12.2, 9.1, 8.6, and 17.7 nmol/mmol, respectively; $P = .003$). Changes in UCCR from baseline levels (ΔUCCR) to week 6 (UCCR week 6 – UCCR at week 0) through week 12 (UCCR at week 12 – UCCR at week 0) were highly significant ($P = .0008$, Kruskal-Wallis test). Corresponding group medians, IQRs, and first and third quartiles for ΔUCCR were –8.9, –20.6, –1.3, and –21.9 nmol/mmol, respectively, at week 6 and –12.6, –25.9, –0.3, and –26.2 nmol/mmol, respectively, at week 12.

Comparing the FP and placebo groups with each other, no significant differences in UCCR were seen at any stage (before treatment, $P = .05$; 6 weeks after treatment, $P = .85$; and 12 weeks after treatment, $P = .10$). Intergroup comparisons in the change of UCCR from baseline levels were insignificant collectively or individually (week 6, $P = .52$; week 12, $P = .19$).

Age at recruitment had no significant effects on intergroup comparisons of UCCR in those younger than and older than 3 months of age (Table II).

TABLE II. UCCRs of infants treated with FP or placebo according to age at recruitment

	Age at recruitment <3 mo				Age at time from recruitment >3 mo				
Time from recruitment	Placebo (nmol/mmol)	n	FP (nmol/mmol)	n	Placebo (nmol/mmol)	n	FP (nmol/mmol)	n	Total
0 wk	22.4 (6.8-315.0)	9	22.0 (0.0-42.7)	7	25.5 (6.3-51.0)	11	25.2 (6.4-65.5)	13	40
6 wk	18.7 (2.1-103.3)	9	10.8 (3.7-30.5)	7	13.4 (2.5-302.5)	11	18.8 (2.9-23.6)	13	40
12 wk	44.6 (4.5-106.3)	9	16.4 (5.4-56.9)	7	14.8 (7.8-61.3)	11	12.0 (2.1-32.5)	13	40

Values are given as medians (ranges). There were no significant differences between age groups.

DISCUSSION

Inhaled corticosteroids are commonly used in infants for the treatment of obstructive airway disease.[10,11] However, information on inhaled dose of drug and possible systemic side effects in young infants are lacking. Our aim was to estimate the total dose of FP inhaled by infants recovering from bronchiolitis when given three 50-μg puffs administered through a spacer fitted with a face mask attachment. The use of a filter interposed between a child and a drug-delivery device has allowed estimations of the amount of total inhaled drug in studies involving older children. Bisgaard[12] reported 19% of the nominal MDI budesonide aerosol dose delivered through a metal holding chamber was available to asthmatic infants with tidal volumes of 19 mL/kg. Similarly, Agertoft and Pedersen[13] found that 19.7% to 27.8% of the nominal pressurized metered dose inhaler budesonide aerosol dose was available to children 10 to 25 months of age by using a number of different spacers. In our study only 8% of the nominal dose of FP was likely to be inhaled by infants after bronchiolitis. This equates, however, to an average dose of 2 μg/kg body weight, which compares favorably with the results reported by Bisgaard.[12] It is of interest that our infants also had small tidal volumes (5.9 mL/kg), possibly because of their recent acute bronchiolitis.

A number of problems arise with the use of filter studies. For example, we found that deposition of FP on the filter increased when infants cried. This is unlikely to represent a true increment in lung deposition because high inspiratory flows during crying are likely to enhance upper airway drug deposition, reducing the amount of drug reaching the lower airways. Indeed, it has been shown that radiolabeled drug deposition in the lung is reduced in crying infants.[14] A small percentage of the drug caught on the filter might be due to a shoot-through phenomenon and not representative of the drug inhaled. That is, on actuation of an MDI, aerosol particles forcefully escaped through the spacer valve, impacting on the filter. Using the spacer, we found that up to 10% of the drug deposited on the filter might have been a result of this phenomenon. Also, filter units might introduce significant dead space to the system. This is particularly important in infants breathing at low tidal volumes. Our filter design introduces virtually no additional dead space.

Ensuring a seal between the face mask and infant can be difficult because of poor cooperation. Most parents in our study used the spacer efficiently. Although infants cried 68% of the time during the tests, no obvious air leak was observed in 95% of actuations. Lack of any FP on 2 of the filters might suggest either a poor seal with the child's face, the child pausing his or her breathing, or sticking of the spacer inlet valve. We made no attempt to control factors such as breath holding, infant cooperation, or parental skill because in real-life situations these factors cannot be easily controlled. Knowledge of the range and variability of inhaled medications under these circumstances is important.

Very little has been published on the systemic effects of inhaled corticosteroids in infancy. In older children receiving inhaled corticosteroids, a suppression of 24-hour urinary cortisol was associated with a blunted dynamic response to low-dose (0.5 μg) adrenocorticotrophic hormone stimulation.[15] Adrenal suppression, particularly low overnight cortisol, is a sensitive marker of systemic bioactivity.[16] Overnight urinary free cortisol measurement in older patients, especially when corrected for creatinine excretion, has been shown to be as sensitive as a 24-hour urine test.[17]

We investigated potential systemic bioactivity of inhaled FP as part of a clinical trial to monitor safety. Data on UCCRs during the first year of life in normal infants is scarce. We have access, however, to overnight UCCRs from a large group of infants from Leicestershire, obtained as part of a separate study. One hundred ninety-eight healthy infants age 6 to 20 weeks (mean, 10.4 weeks) had overnight urine samples collected: UCCR levels were 12.2 nmol/mmol (median), 11.5 nmol/mmol (mean), and 2.6 to 45.8 nmol/mmol (± 2 SD from the mean; personal communication from Drs Tim Davies and Mike Wailoo, University of Leicester). In a longitudinal study of 29 normal infants between 7 and 16 weeks of age, mean ± SEM overnight UCCRs were 16.14 ± 4.5 between 6 and 8 weeks of age and 12.29 ± 2.0 between 12 and 14 weeks of age.[18]

UCCR is likely to decrease during infancy, and a number of surrogate biomarkers have suggested this. Salivary cortisol levels, which closely reflect plasma free cortisol levels,[19] have been shown to decrease progressively with

age in infants 1 to 30 weeks old.[20] By 12 weeks of age, a decrease in salivary free cortisol levels[20] and UCCRs[18] can be seen, which is consistent with commencement of adult-like circadian rhythm. Infants at this age (mean, 4.8 months) have similar plasma cortisol levels,[21] free and bound, as those of older children. Therefore during the first 3 months of life, there is a change in the adrenal function and handling of cortisol toward an adult pattern. After 3 months of age, UCCRs stop decreasing, reaching adult levels, and possibly can be more reliably used as a tool to monitor adrenal function. In our study we were not able to make comparisons with normal age-adjusted UCCR values. Comparing the FP and placebo groups, statistical differences in UCCRs were found only at week 12. Age at recruitment had no significant effects on the intergroup comparisons of UCCR in those younger than and older than 3 months of age (Table II). Longitudinal change of UCCR over the 3-month treatment period was only significant in the FP group. UCCRs decreased significantly in the FP group over the 12-week treatment period, and the CI was narrower than that in the placebo group. UCCRs remained high in the placebo group despite relatively low symptom scores.[1] Hanukoglu et al[22] also reported high levels of basal and stimulated cortisol in infants (1-4 months old) recovering from acute bronchiolitis, both of which decreased by 50% over several weeks. A similar percentage decrease in UCCR levels was seen in our study during the first 6 weeks in both treatment groups. The subsequent increase of UCCR in the placebo group by week 12 does not fit the expected pattern of change after bronchiolitis or that expected from maturing normal infants. Interestingly, UCCR levels at week 12 were significantly different between FP-treated and placebo-treated infants. To explore whether our study might have been affected by type II error, we performed a retrospective sample size calculation. To show statistical significance in UCCRs with 80% power, we would have needed 7.5 times more patients in the placebo group (n = 148) than in the FP group (n = 20). Alternatively, an equal sample size of 105 infants in each group would be required.

It is possible that the amount of FP inhaled was too small to make physiologic differences. In our report of the clinical trial,[1] we have shown no differences in respiratory symptoms, ciliary recovery, and height or weight percentiles between the FP and placebo groups over the 3-month treatment period. It might be suggested that the amount of drug delivered was inadequate. However, the dose chosen was already considered high, and we would not recommend a higher one. Although treatment with FP did not suppress UCCRs below values seen in our local data (personal communication, Dr M. Wailoo) it is not possible to draw any overall conclusions relating to the safety of FP in the dosage we gave. We do not know whether UCCRs will continue to decrease beyond the 12-week inhaled FP treatment time we chose. It is likely that inhaled steroids are ineffective in infants recovering from bronchiolitis in accordance with other reports.[2,3] Our data, however, suggest that there is delivery of inhaled steroids through the spacer device used, which is comparable with reports from other studies using spacer devices.[12] This is supported by the effect of urinary steroid excretion. Therefore the device might be useful in the delivery of steroids in other conditions, such as asthma. Continued pharmacovigilance is recommended until further data are available.

In this report we estimated that the total dose of FP inhaled by infants recovering from bronchiolitis through a Babyhaler spacer with face mask was 8% of the prescribed dose. We also described a simple method for obtaining urine to measure UCCRs in young infants treated with inhaled corticosteroids. During a 3-month treatment period with FP delivered through the Babyhaler spacer, a significant trend of decrease in UCCR was found only within the FP group but not in comparison with that seen in the placebo group. Further studies are required to clarify the safety of inhaled FP during infancy and the use of UCCRs to monitor safety. Inhaled corticosteroids are unlikely to be beneficial in the treatment of bronchiolitis during the acute and recovery phases.

We thank the infants and their parents for their willingness to take part in this study. We also thank Dr Peter Barry and Mrs Judith Jackson of the Medical Aerosol Research Laboratory (Department of Child Health, University of Leicester) for providing the fluticasone HPLC analysis.

REFERENCES

1. Wong JY, Moon S, Beardsmore C, O'Callaghan C, Simpson H. No objective benefit from steroids inhaled via a spacer in infants recovering from bronchiolitis. Eur Respir J 2000;15:388-94.
2. Springer C, Bar-Yishay E, Uwayyed K, Avital A, Vilozni D, Godfrey S. Corticosteroids do not affect the clinical or physiological status of infants with bronchiolitis. Pediatr Pulmonol 1990;9:181-5.
3. Cade A, Brownlee KG, Conway SP, Haigh D, Short A, Brown J, et al. Randomised placebo controlled trial of nebulised corticosteroids in acute respiratory syncytial viral bronchiolitis. Arch Dis Child 2000;82:126-30.
4. Goodwin A. An uncontrolled assessment of nebulised budesonide in the treatment of acute bronchiolitis. Br J Clin Res 1995;6:113-9.
5. Reijonen T, Korppi M, Kuikka L, Remes K. Anti-inflammatory therapy reduces wheezing after bronchiolitis. Arch Pediatr Adolesc Med 1996;150:512-7.
6. Carlson KH, Leegard J, Larsen S, Orstavic I. Nebulised beclomethasone dipropionate in recurrent obstructive episodes after acute bronchiolitis. Arch Dis Child 1988;63:1428-33.
7. Fox GF, Everard ML, Marsh MJ, Milner AD. Randomised controlled trial of budesonide for the prevention of post-bronchiolitis wheezing. Arch Dis Child 1999;80:343-7.
8. Lipworth BJ, Seckl JR. Measures for detecting systemic bioactivity with inhaled and intra nasal corticosteroids. Thorax 1997;52:476-82.
9. Court SDM. The definition of acute respiratory illness in children. Postgrad Med J 1973;49:771-6.
10. de Blic J, Delacourt C, Le Bourgeois M, Mahut B, Ostinelli J, Caswell C, et al. Efficacy of nebulized budesonide in treatment of severe infantile asthma: a double-blind study. J Allergy Clin Immunol 1996;98:14-20.
11. Scott MB, Skoner DP. Short-term and long-term safety of budesonide inhalation suspension in infants and young children with persistent asthma. J Allergy Clin Immunol 1999;104(suppl):200-9.
12. Bisgaard H. A metal aerosol holding chamber devised for young children with asthma. Eur Respir J 1995;8:856-60.
13. Agertoft L, Pedersen S. Influence of spacer device on drug delivery to young children with asthma. Arch Dis Child 1994;71:217-20.
14. Tal A, Golan H, Grauer N, Aviram M, Albin D, Quastel NR. Deposition pattern of radiolabelled salbutamol inhaled by a metered dose inhaler by means of a spacer with mask in young children with airway obstruction. J Pediatr 1996;128:479-84.
15. Broide J, Soferman R, Kivity S, Golander A, Dickstein G, Spirer Z, et al.

Low dose adrenocorticotrophine tests reveal impaired adrenal function in patients taking inhaled corticosteroids. J Clin Endocrinol Metab 1995;80:1243-6.
16. Lipworth BJ, Seckl JR. Measures for detecting systemic bioactivity with inhaled and intra nasal steroids. Thorax 1997;52:476-82.
17. McIntyre DH, Mitchell CA, Bowler SD, Armstrong JG, Wooler JA, Cowlie DM. Measuring the systemic effects of inhaled beclomethasone: timed morning urine collections compared with 24 hours specimens. Thorax 1995;51:281-4.
18. Petersen SA, Atkinson C, Davies T, Wailoo MP. Relationship between daily rhythms of rectal temperature and cortisol excretion in human infants [abstract]. Proc Physiol Soc 1994;85P:85P.
19. Umeda T, Hiramatsu R, Iwaoka T, Shimada T, Miura F, Soto T. Use of saliva for monitoring unbound free cortisol levels in serum. Clin Chim Acta 1981;110:245-53.
20. Price DA, Close GC, Fielding BA. Age of appearance of circadian rhythm in salivary cortisol values in infancy. Arch Dis Child 1983; 58:454-6.
21. Sippell WG, Dorr HG, Bidlingmaier F, Knorr D. Plasma levels of aldosterone, corticosterone, 11-deoxycorticosterone, progesterone, 17-hydroxyprogesterone, cortisol, and cortisone during infancy and childhood. Pediatr Res 1980;14:39-46.
22. Hanukoglu A, Fried D, Nakash I, Hanukoglu I. Selective increases in adrenal steroidogenic capacity during acute respiratory disease in infants. Eur J Endocrinol 1995;133:552-6.