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No objective benefit from steroids inhaled *via* a spacer in infants recovering from bronchiolitis

J.Y.W. Wong, S. Moon, C. Beardsmore, C. O'Callaghan, H. Simpson

No objective benefit from steroids inhaled via *a spacer in infants recovering from bronchiolitis. J.Y.W. Wong, S. Moon, C. Beardsmore, C. O'Callaghan, H. Simpson. ©ERS Journals Ltd 2000.*

ABSTRACT: A double-blind randomized placebo-controlled trial was conducted to investigate the efficacy of 3 months' inhaled steroids delivered *via* a spacer device with face mask attachment to infants recovering from bronchiolitis.

Forty-eight previously healthy infants recovering from their first documented episode of acute bronchiolitis were randomized to receive 150 μg fluticasone propionate (FP) *b.i.d.* or placebo delivered *via* the Babyhaler spacer. Longitudinal assessments were performed on seven occasions over 1 yr based on symptom diaries and health records, clinical examinations, overnight cough recordings and oxygen saturation readings. Lung function was measured 6 months after hospital discharge. Forty-three infants completed the trial (FP 21, placebo 22).

There were no significant differences in the three objective end-points measured, recorded night cough, oxygen saturation and lung function test results. Symptom scores were low in both the FP and placebo groups with the absence of (0) or mild (1) symptoms ≥90% of the trial days. No statistical differences in symptom frequency, use of rescue respiratory medications or hospital admissions between treatment groups were found throughout the trial or follow-up periods.

In conclusion, the use of inhaled fluticasone propionate in infants recovering from acute bronchiolitis cannot be recommended.

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Dept of Child Health, University of Leicester, Leicester Royal Infirmary, Leicester, UK.

Correspondence: C. O'Callaghan, Dept of Child Health, University of Leicester, Clinical Sciences Building, Leicester Royal Infirmary, P.O. Box 65, Leicester LE2 7LX, UK. Fax: 44 1162523282

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Bronchiolitis, usually caused by respiratory syncytial virus (RSV), is the commonest lower respiratory tract infection in infancy. The salient symptoms include cough, wheeze and dyspnoea, associated with hyperinflation of the chest, intercostal recession and fine crepitations on auscultation. Up to 75% of affected infants have wheezy episodes during the 2 yrs following apparent clinical recovery [1] and >40% of these infants still cough or wheeze 6 yrs later [2–5]. Symptoms decrease further with age [6–12]. Most investigators have found raised respiratory resistance, reduced compliance and evidence of airway obstruction in infants during the acute bronchiolitic illness [13–18], but the picture is less clear during the follow-up period. Despite persistence of respiratory symptoms, normal lung function and airway responsiveness have been reported within 6 weeks of the acute illness [3, 13, 14, 19, 20]; other investigators have found abnormal lung function some years following bronchiolitis [7, 8, 10–12, 16]. Whether such abnormalities can be attributed to bronchiolitis or pre-existing defects in the small airways is not clear [21]. Abnormal airway responsiveness within the first 6 yrs following bronchiolitis [3, 4, 22, 23] has also been reported.

Despite the many infants admitted to hospital with severe lower respiratory tract disease due to bronchiolitis, the main treatment is general supportive care and relief of hypoxaemia. There is little evidence to support the routine use of any drug treatment, including corticosteroids, in acute bronchiolitis [24–30]. Inhaled steroids have been given after the acute infection in an attempt to reduce subsequent morbidity. Some such studies have focused on selected groups of infants with persistent respiratory symptoms recruited some months after hospital discharge following their acute bronchiolitic illness [31, 32]. One study included young children who might have had early asthma [32]. Others were either unblinded [33] or lacked objective physiological end-points [34, 35]. None of these studies attempted to assess compliance or the dosage of inhaled steroids available to infants following bronchiolitis. The negative results may have been secondary to the drug delivery device chosen [34].

Given the high level of morbidity in infants following hospitalization due to acute bronchiolitis [1–12], inhaled steroids were introduced immediately following hospital discharge. The aim was to assess their efficacy and safety during the trial period, and possible beneficial effects during the following 9 months.

Methods

Patients and ethical approval

Forty-eight infants aged 2 weeks–12 months were recruited during two bronchiolitis seasons (March 1994–April 1996). All infants were patients in the paediatric wards at the Leicester Royal Infirmary with their first

episode of lower respiratory tract infection. They had no previous history of wheeze or respiratory illnesses apart from mild upper respiratory symptoms. One investigator (J.Y.W. Wong) diagnosed acute bronchiolitis using the criteria suggested by COURT [36]. Nasopharyngeal aspirates were sent for immunofluorescent study and viral culture. Exclusion criteria were: birth before 36 weeks of gestation; congenital heart disease or syndromic abnormalities; established systemic or chronic illnesses; and treatment with corticosteroids or mechanical ventilation before entering the study. Parents were contacted before hospital discharge and written informed consent obtained from those who agreed to their children entering the study. Parents were taught how to use the inhaler/ Babyhaler (Glaxo, Greenford, UK) combination, and those who were unable to master the technique were excluded. A detailed history was obtained for each of the remaining infants and documented together with examination findings and treatment(s). The study was approved by the local ethics committee.

Study protocol

Infants were selected for the study just before hospital discharge and entered into a single-centre double-blind randomized placebo-controlled parallel-group trial. They were randomized to receive either placebo or fluticasone propionate (FP) from a metered dose inhaler (MDI) (three puffs of 50 μg FP *b.i.d.*) for 3 months, administered *via* the Babyhaler (a low-volume spacer) with a face mask attachment. Home visits took place after 3 and 6 weeks, and then at 3, 6, 9 and 12 months after hospital discharge. Clinical decisions about the need for additional treatment(s) were made solely by family practitioners and/or hospital doctors.

Quantification of cough by means of overnight tape recordings was chosen to provide an objective but necessarily infrequent measure of night symptoms. A significant change in cough rate from pretreatment baseline levels was sought. Precise power calculations were not possible as there were no previous data available regarding night cough counts in infants recovering from acute bronchiolitis.

Other assessments of the effects of inhaled FP on bronchiolitis were based upon diary records of symptoms completed by parents and overnight oxygen saturation measurements. Pulmonary function and bronchial reactivity testing were also performed 3 months after completion of the trial medications.

Parents were asked to record symptoms twice daily on diary cards during the 3-month treatment period. Thereafter, they recorded symptoms for the 2-week periods immediately preceding 3-monthly reviews. Cough, wheeze and general well-being were scored 0–3 (0=none, 1=mild, 2=troublesome, and 3=severe) for both day and night. The use of MDIs was also recorded and MDIs weighed every 3 weeks before the next MDI was issued. The mean compliance of patients in each group was calculated separately for the diary and MDI weight losses. Family doctor and hospital records were examined at the end of the study for corroborative information.

The safety of the inhaled steroid therapy was assessed by means of periodic clinical examinations and measurement of length, weight and blood pressure using standard measurement devices appropriate for infants. Crown–heel length was measured by two persons (J.Y.W. Wong and S. Moon) using a stadiometer. Two recordings within 0.5 cm of each other were accepted and the mean value calculated. Cortisol/creatinine ratios were measured in the urine collected overnight at each visit during the treatment period; the results will be reported separately.

Home monitoring

The Nellcor-3000 pulse oximeter (Nellcor Puritan Bennett, Pleasanton, CA, USA) was used to monitor overnight arterial oxygen saturation (S_{a,O_2}). An on-line notebook computer using the SatMaster programme (EMG Scientific, Beverly Hills, CA, USA) captured beat-to-beat S_{a,O_2} and pulse rate data. A disposable Nellcor Oxisensor II sterile single-use N-25 oximeter probe (Nellcor Puritan Bennett) was attached to the infant's big toe in the afternoon, in preparation for overnight monitoring. Trend data, pulse oximetry S_{a,O_2} recorded every 10 s, were downloaded from the oximeter the following morning.

Cough monitoring was performed as previously described [37]. The system was tested in the home and parents had simply to switch on a voice-activated tape recorder and connect the oximeter to the infant on monitoring nights. The duration of cough and overnight S_{a,O_2} monitoring were read simultaneously the following morning.

Cough tapes were analysed aurally and simultaneously through a British Broadcasting Corporation computer (Acorn Computers, cambridge, UK), with print out of cough events and episodes. The former refers to single cough and the latter to a period of coughing with $\geq$10 s silence before and after, reported as events or episodes·h^{-1}.

Infant lung function

Infant lung function tests were performed 3 months after the end of the treatment period. On arrival at the lung function laboratory, the recent history was taken and the infant examined. S_{a,O_2} was measured to ensure that the infant was not hypoxaemic and fit for sedation (S_{a,O_2} >95%). Infants were then sedated with chloral hydrate up to a total of 100 mg·kg body weight^{-1}. When asleep, the infant was placed within the whole-body plethysmograph for measurement of functional residual capacity (FRC_{pleth}) and airways resistance (R_{aw}). The infant breathed through a face mask and pneumotachograph, which was attached to a block containing two pneumatically controlled valves which could be used to switch the infant from breathing room air within the plethysmograph to breathing heated humidified air from a rebreathing bag as R_{aw} was measured. These valves could also be closed simultaneously at end-inspiration for two or three respiratory efforts during the measurement of FRC_{pleth}. Where possible, five or six technically satisfactory measurements of both R_{aw} and FRC_{pleth} were made according to a predetermined protocol [38]. Airways conductance (G_{aw}), the reciprocal of R_{aw}, was calculated and the values of FRC_{pleth} and G_{aw} were compared with those predicted on the basis of mean infant length.

Measurements of maximum flow at functional residual capacity ($V'_{max,FRC}$) were then made using the technique of rapid thoracoabdominal compression (RTC) [39]. In brief, a plastic double-walled jacket which could be inflated at the end of tidal inspiration was wrapped around the chest and abdomen. The arms were within the jacket

and the infant breathed through a pneumotachograph and face mask positioned over the nose and mouth, permitting the recording of respiratory flow and volume. Inflating the jacket produced a firm squeeze which did not disturb the infant but caused rapid exhalation, producing a partial maximal expiratory flow/volume curve. The RTC manoeuvre was repeated several times for each infant using a range of applied pressures.

Bronchial responsiveness was measured by means of histamine challenge in those infants who showed no evidence of wheezing and in whom baseline recordings of the maximum expiratory flow were clearly separated from those of tidal flow. Initially, infants received nebulized saline (0.9%) for 2 min, and then measurements of $V'_{max,FRC}$ were repeated. Histamine was then given at 5-min intervals in doubling doses, commencing at 0.25 $g \cdot dL^{-1}$. Following each inhalation, three measurements of $V'_{max,FRC}$ were made. The histamine challenge stopped when there was a fall in $V'_{max,FRC}$ of $\geq$30% (PC_{30}), or the maximum dose of 16 $g \cdot dL^{-1}$ was reached. Log concentrations of histamine were used to calculate PC_{30} [40].

Statistical methods

Statistical analysis was performed on an intention-to-treat basis, unless specified, as there was no obvious problem with compliance. Changes in cough rate (cough events$\cdot h^{-1}$ and cough episodes$\cdot h^{-1}$) measured both before and after treatment were examined. Since the time intervals between overnight cough recordings were not equally spaced, the weighted mean change (WMC) in cough rate was used to compare reductions in cough rate between treatment groups. Treatment effects between treatment groups were assessed using the Wilcoxon test. Median values and 95% confidence levels for infants' WMCs in cough rate were calculated. The WMC in cough rate for each infant was calculated using the trapezium rule. The area under the curve (AUC) for each infant's overnight cough rate were assessed between consecutive home monitoring visits to the home visit of interest. The AUC between visit 1 and visit 4 (the end of the 12-week inhaled therapy) is represented by:

$$AUC = \frac{d_2(C_2 + C_1) + d_3(C_2 + C_3) + d_4(C_3 + C_4)}{2d_1}$$

where C is the change in cough rate (events$\cdot h^{-1}$ or episodes$\cdot h^{-1}$), C_1 the change from baseline at visit 1 (=0), C_2 the change from baseline at visit 2, C_3 the change from baseline at visit 3, C_4 the change from baseline at visit 4, d_2 the number of days between visits 1 and 2, d_3 the number of days between visits 2 and 3, d_4 the number of days between visits 3 and 4, and d_1 the number of days between visits 1 and 4.

For each infant, the WMC is equal to the sum of all AUCs of interest divided by the time from baseline (week 0) recording to the end of the 3-month treatment period (week 12). The same calculation was repeated for the period from baseline until 6 months after stopping treatment. Although all infants were followed for 9 months after treatment ceased, the cough data for the final 3 months were not analysed to avoid confounding effects of the second bronchiolitis season.

The proportion of days on which each symptom score was present was examined. The percentage of entered diary days with symptom scores of 0, 1, 2 and 3 were calculated for each infant during the treatment period, and expressed as group median values with 95% confidence intervals. Differences between groups were assessed by the Wilcoxon test. The Bonferroni correction was made to adjust for multiple testing [41].

S_{a,O_2} data were analysed by calculating the percentage of S_{a,O_2} values of <90% and <94%. Since any differences in overnight S_{a,O_2} were expected to be present early in the study, the placebo and steroid groups were only compared during the first 3 weeks.

The two-sided Fisher's exact test was used to assess whether there were any significant differences in prescribed medications for respiratory events between treatment groups.

Standard error scores [42] were calculated for FRC_{pleth}, G_{aw} and $V'_{max,FRC}$. PC_{30} was calculated according to COCKCROFT and BERSCHEID [40].

Drug delivery and compliance

Drug availability was assessed in a further 22 infants hospitalized because of acute bronchiolitis. For each 150 mg dose of FP, the amount that would have been inhaled was determined by placing a filter within the face mask of the Babyhaler device [43] during *in vivo* inhalations.

Compliance in administering the inhaler in the FP group was checked by examining diary cards and changes in the weights of the inhalers used. MDI compliance was also examined longitudinally on a 3-weekly basis, when new inhalers were issued, and weight loss determined in those returned.

Results

Twenty-four infants in each treatment group entered the study during the bronchiolitis season 1994–1996. The demographic data were similar in the two groups (table 1). Twenty-one infants in the FP group (nine RSV-positive) and 22 in the placebo group (10 RSV-positive) completed the trial. Three infants in the FP group were withdrawn. Two, distressed by the application of the face mask, were withdrawn within the first 10 days, and the third after 5 weeks of treatment for "social" reasons. Four infants in the placebo group were withdrawn, two during the treatment period. One was accidentally given FP by the hospital dispensary after receiving placebo for 6 weeks and another was started on prophylactic inhaled steroids 2 months after recruitment, following repeated hospital admissions for episodes of wheeze. The two post-treatment withdrawals were for noncompliance and change of domicile to another region. The symptom diary of the latter case was available for scrutiny.

Overnight cough recordings

Overnight cough recordings were attempted on every visit. During the treatment period, 87% of attempted night cough recordings were technically successful (FP 88% (77/88); placebo 86% (81/94)). On a further 10 nights, cough monitoring was not attempted due to patient withdrawal

Table 1. – Demographic data of the fluticasone propionate (FP) and placebo group

	FP	Placebo
Subjects n	24	24
Sex M/F	13/11	14/10
Gestation weeks	39.4 (36.8–43.0)	39.7 (36.0–42.0)
Weight centile	43.8 (2–97)	37.3 (2–98)
Length centile	47.5 (0.4–91)	42.2 (2–99.6)
Age months	3.8 (0.9–4.7)	3.9 (1.0–10.9)
Race		
Caucasian	19	19
Other	5	5
Family history		
Eczema (index case)	5	6
Asthma in mother	4	4
Eczema in mother	3	7
Rhinitis in mother	3	5
Exposure to smoking		
Passive	15	15
Parental cigarettes·day^{-1}	12.7 (0–40)	8.5 (0–40)
Breast fed (ever)	8	11
RSV	10	10
Other virus	1	3
Oxygen therapy	10	12
NG/*i.v.* feed	8	11
Days into illness on admission	3.7 (1–7.5)	3.8 (1.5–7.5)
Hospital stay days	3.2 (1–6.5)	3.5 (1–8.5)

Data are presented as n or mean (range). Respiratory syncytial virus (RSV) and other virus refer to positive results on nasopharyngeal aspirate immunofluorescent test and/or viral culture. M: male; F: female; NG: nasogastric.

(FP eight; placebo two). During follow-up, 88% (113/129) of cough recordings were successful (FP 91% (57/63); placebo 85% (56/66)). Cough recordings were not attempted on 15 occasions (FP nine; placebo six) due to patient withdrawal. A total of 271 successful night cough recordings were performed over the 12-month trial period with a mean±SD recording duration of 8.8±2.1 h·night^{-1}.

Initially, before the trial inhalers were issued, the median values for cough rates (FP: n=22; placebo: n=23) were similar: cough episodes·h^{-1}: FP 0.8, placebo 0.6; and cough events·h^{-1}: FP 3.5, placebo 3.1. At the end of the treatment period, the median cough rates (FP: n=18; placebo: n=19) were: cough episodes·h^{-1}: FP 0.05, placebo 0.10; and cough events·h^{-1}: FP 0.09, placebo 0.22, (NS). Table 2 presents the cumulative changes in cough rate for the placebo and FP groups during the treatment and follow-up periods (up to 36 weeks). Intergroup differences in overnight cough episodes and events related to these changes were unremarkable, during both treatment and follow-up periods, and only significant at 36 weeks (p=0.05) for cough episodes. In table 2, missing data at 12 and 36 weeks were filled by extrapolating previous visits′ data. Patients with no data following the baseline cough recordings were eliminated from the analysis. The trends and p-values in table 2 were similar with or without data extrapolation. Figure 1 shows the percentage of infants who were cough-free at each home visit, for the total study period. There were no statistically significant differences.

Symptoms and clinical findings

Three-month treatment period. The diary cards were examined for symptom scores, the prescription of medications (β_2-agonists, corticosteroids and antibiotics) and respiratory "events", defined arbitrarily as an increase in respiratory symptoms that led carers to seek medical advice.

The median (95% confidence interval) number of days on which scores (0, 1, 2 and 3) were entered on the diary cards were 84.0 (82.0–86.0) for FP infants and 83.5 (81.7–85.0) for those on placebo. Table 3 shows the median (and 95% confidence intervals) percentage of days with symptom scores of 0, 1 and 2. The medians for a score of 3 were zero.

In order to assess the need for additional prescribed medications, infants withdrawn from the study were included in the analysis up to the day of their withdrawal.

Table 2. – Cumulative changes in cough rate in the placebo and fluticasone propionate (FP) groups during treatment and follow-up

	Change in cough rate		Patients n		p-value^{+}
Time from baseline wks	FP	Placebo	FP	Placebo	
Cough events·h^{-1}					
Treatment					
3	-0.12 (-0.69–-0.00)	-0.27 (-0.44–-0.01)	21	23	
6	-0.57 (-2.05–-0.04)	-0.76 (-1.64–-0.15)	21	23	
12*	-1.79 (-5.81–-0.16)	-1.99 (-4.50–-0.38)	21	23	0.64
Follow-up					
24	-1.64 (-5.43–-0.32)	-0.96 (-3.22–-0.23)	20	21	
36*	-3.09 (-8.95–-0.75)	-1.72 (-5.09–-0.08)	20	21	0.20
Cough episodes·h^{-1}					
Treatment					
3	-0.00 (-0.15–-0.00)	-0.01 (-0.06–-0.00)	21	23	
6	-0.17 (-0.36–-0.00)	-0.07 (-0.18–-0.02)	21	23	
12*	-0.58 (-1.05–-0.02)	-0.15 (-0.46–-0.01)	21	23	0.16
Follow-up					
24	-0.48 (-0.93–-0.03)	-0.12 (-0.33–-0.06)	20	21	
36*	-0.71 (-1.52–-0.06)	-0.19 (-0.58–0.05)	20	21	0.05

Data are presented as group median values (95% confidence interval) of weighted mean changes from baseline using the area under the curve method. Negative values indicate less cough compared with pretreatment cough rates. *: missing data at weeks 12 and 36 were extrapolated from those of the previous visit; $^{+}$: Wilcoxon test.

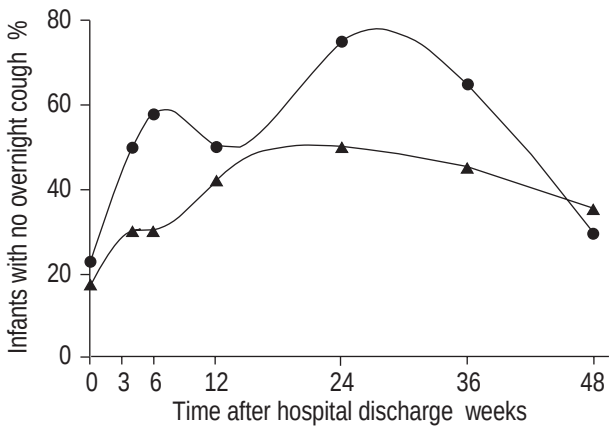

Fig. 1. – Percentage of infants who were cough-free at each home visit during the total study period (●: fluticasone propionate group; ▲: placebo group). The study comprised pretreatment at week 0 followed by a 12-week treatment period and then a 36-week follow-up period.

More infants in the placebo group received bronchodilators/steroids (placebo eight of 24, FP two of 24 (two-sided Fisher′s exact test p=0.07)) but not antibiotics (placebo 11 of 24, FP 10 of 24).

Respiratory "events", *i.e.* the proportions of infants for whom medical advice was sought, were similar in both treatment groups (placebo 15 of 24; FP 13 of 24). Initially, 19 of 24 infants in the placebo group and 20 of 24 in the FP group wheezed on clinical examination. After 3 months′ therapy, the corresponding figures were 7 of 22 and 4 of 21.

Nine-month post-treatment period. During follow-up, the frequencies of cough, wheeze and well-being symptom scores were not significantly different. The numbers of infants who received treatment (FP 12; placebo 12), experienced respiratory "events" (FP 19; placebo 19) or were admitted to hospital (FP one, placebo two) were similar in the FP and placebo groups. One infant in the FP group and three in the placebo group wheezed on clinical examination.

Oxygen saturation

Overnight S_{a,O_2} was measured at each visit throughout the trial. The median (range) values before therapy were 95% (91–98%) for the FP group and 96% (90–97%) for the placebo group. There were no differences in median S_{a,O_2} during the early weeks of therapy or at any time thereafter. The percentage of overnight S_{a,O_2} levels of <94% and <90% were similar for both the treatment and placebo groups during the first 3 weeks of therapy.

Table 3. – Percentages of days with symptom scores of 0, 1 and 2 in the fluticasone propionate (FP) and placebo groups

Symptom score category	FP Median (95% CI)	Placebo Median (95% CI)	p-value
Cough 0	58.9 (50.5–73.8)	39.1 (28.5–56.3)	0.011
Cough 1	30.9 (23.8–43.2)	41.0 (34.4–51.8)	0.075
Cough 2	4.2 (0.6–7.9)	10.4 (3.0–17.0)	-
Wheeze 0	87.7 (73.1–6.6)	53.9 (46.5–76.3)	0.009
Wheeze 1	11.0 (3.4–20.6)	32.2 (12.9–44.7)	0.011
Wheeze 2	0.3 (0.0–1.9)	5.5 (0.6–12.7)	-
Well-being 0	81.6 (69.0–93.1)	68.6 (46.5–90.8)	0.009
Well-being 1	14.0 (6.8–27.7)	26.7 (8.5–34.9)	0.011
Well-being 2	1.8 (0.0–3.6)	3.6 (1.0–8.5)	-

There were no significant changes in cough, wheeze and well-being following Bonferroni correction of initial p-values. CI: confidence interval.

Lung function

Technically satisfactory baseline measurements of FRC_{pleth} and $V'_{max,FRC}$ were available for 19 infants from the FP group and 21 from the placebo group. Satisfactory measurements of R_{aw} (and hence of G_{aw}) were available for 18 infants from each group.

Infants in both treatment groups tended to have reduced FRC_{pleth} and G_{aw} (corresponding to a higher R_{aw}) and a lower $V'_{max,FRC}$ than predicted on the basis of body length [42]. These measurements are expressed as a standard error score for each infant to facilitate comparison of data from infants of different body length (fig. 2). A standard error score outside the 2– -2 range is assumed to represent a significant difference from the predicted value for normal infants. There were no differences between the two groups for any of the measurements shown (p=0.07 for FRC_{pleth}, 0.38 for G_{aw} and 0.42 for $V'_{max,FRC}$).

Most infants were excluded from histamine challenge testing because baseline measurements of $V'_{max,FRC}$ were markedly reduced, such that there was little difference between forced expiratory flow and tidal flow rates. Five infants from each group were successfully challenged. The geometric mean PC_{30} was 3.10 $g \cdot dL^{-1}$ for the FP group and 0.89 $g \cdot dL^{-1}$ for the placebo group.

Side effects

No fungal infections occurred during the treatment period. Two infants in the FP group developed oral candidiasis during follow-up. There were no significant differences between treatment groups in length, weight and systolic blood pressure centiles measured during the treatment period and 6 months after the start of the trial.

Drug delivery

The *in vivo* drug inhalation study showed that a mean of 12.15 μg (95% confidence interval 9.64–14.7) FP was

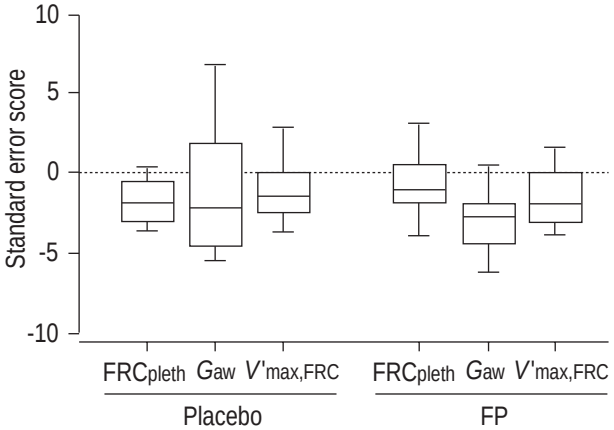

Fig. 2. – Standard error scores for lung function measurements in infants in the placebo and fluticasone propionate (FP) groups. Data are presented as median and 25th and 75th centiles of standard error scores, with vertical bars representing 95% confidence intervals. FRC_{pleth}: functional residual capacity (FRC) measured within a whole-body plethysmograph; G_{aw}: airways conductance; $V'_{max,FRC}$: maximum flow at FRC.

captured on the filter paper interposed between the infant and the spacer device for each 150 μg dose.

Compliance

Table 4 shows that during the trial period compliance rates of 93 and 84% were obtained from diary card and MDI weight loss computation respectively. The mean±SD numbers of actuations were 112±97 for weeks 1–3, 129±43 for weeks 7–9 and 87±49 for weeks 10–12. There was a fall in the use of inhalers during the last 3 weeks of FP therapy.

Discussion

The effects of inhaled steroids, given immediately following acute bronchiolitis, on respiratory morbidity were investigated in a double-blind placebo-controlled trial. The results of objective measures of assessment (recorded night cough frequency, S_{a,O_2} and post-trial lung function test) were not significantly different in the FP and placebo groups. Although there was an apparent reduction in symptoms in the FP group during the treatment period, this was not significant when statistical correction was applied for multiple p-values. During follow-up, no differences were observed for cough, wheeze and well-being.

No statistical differences were found in overnight recorded cough frequency. Cough rates were unlikely to have been spuriously increased as infant cough was distinguishable from parental cough and other environmental noises. Underrecording may have occurred due to temporary suspension of recordings in some infants awakened by night-time symptoms. Unfortunately, an accurate power calculation was not possible before the trial. The data showed that 58% of the infants in the placebo group coughed at night at the end of the 3-month trial period. To demonstrate a 50% improvement, *i.e.* only 29% continuing to cough, with a power of 0.8 would have required 90 infants. The infrequent recording of cough, made necessary by practical considerations, limits further the interpretation of the results obtained.

Median S_{a,O_2} was similar in the FP and placebo groups during the trial period, including the proportion of infants with low S_{a,O_2}. These findings are hardly surprising as S_{a,O_2} measurements were mainly within the normal range at the start of the trial, with relatively few infants in either group with low S_{a,O_2}, despite the persistence of symptoms. There was thus limited scope for improvement with treatment. Similarly, assessment of lung function 3 months after completion of treatment showed no differences between the FP and placebo groups, although some infants in each group had lower lung volumes, higher R_{aw} and greater airflow limitation than normal infants [40]. This is consistent with the suggestion that pre-existing abnormal lung function influences the occurrence and severity of bronchiolitis [21]. Inhaled steroids may be ineffective in such cases. Unfortunately, bronchial responsiveness was assessed in too few subjects to allow meaningful comparisons.

Table 4. – Compliance with treatment in the fluticasone propionate group

Diary records	
Intention to give MDI days	76 (6–90)
MDI given days	73 (5–88)
Compliance %	93 (48–100)
MDI weight loss*	
MDI actuated days	63 (5–110)
Compliance %	84 (45–138)

Data are presented as mean (range). *: metered dose inhaler (MDI) actuation was calculated from inhaler weight loss; compliance exceeded 100% in some infants, possibly due to MDI overuse.

For each symptom assessed, scores of 0 and 1 predominated, and the percentage of days with higher scores was generally <10. Following Bonferroni corrections, no statistical differences were found between treatment groups, confirming the results of previous studies of inhaled corticosteroids given during recovery from acute bronchiolitis [33–35]. None of these studies included objective measures of assessment, information about probable drug delivery or estimates of compliance with treatment. In addition, the first was unblinded [33], and the second employed a SideStream nebulizer (Medic-Aid, West Sussex, UK) to deliver budesonide with no information about its effectiveness [34]. In the third study, a Nebuhaler (AstraZeneca Pharamaceuticals, Kings Langley, UK) delivery system was used [35], its possible effectiveness prediction being based on a study in older children [44].

In the present study, sample size was small. It is of interest, however, that according to the power calculation of RICHTER and SEDDON [34], based in the percentage reduction of reported incidence of wheeze, the present study would have included sufficient infants. The amount of FP likely to have been inhaled per 150 μg dose was small and might account for the failure to demonstrate a therapeutic effect. The proportion of each dose delivered to the peripheral airways is not known. Throughout the trial, compliance with inhaler administration was good but fell off during the final weeks of the trial, with possible effects on symptom scores and night cough rate results.

In conclusion, inhaled fluticasone propionate did not influence recorded night cough, arterial oxygen saturation or lung function following acute bronchiolitis. Similarly, no differences were observed for diary and symptom scores, rescue medications or hospital admission, during the treatment and follow-up periods. Whether this reflects inadequate drug delivery or ineffectiveness of inhaled fluticasone propionate is not known. At present, the use of inhaled fluticasone propionate in infants immediately following acute bronchiolitis is not recommended.

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