Fluticasone Inhalation in Moderate Cases of Bronchopulmonary Dysplasia

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ABSTRACT. *Objective.* **This randomized, controlled trial was designed to determine the efficacy of inhaled fluticasone propionate on oxygen therapy weaning in a population of preterm infants who were born at <32 weeks of gestation and experienced moderate bronchopulmonary dysplasia (BPD).**

Methods. **Thirty-two infants who were ≤32 weeks of gestation, had moderate BPD that required supplemental oxygen (fraction of inspired oxygen ≥0.25), and were aged between 28 and 60 days were randomized. Fluticasone propionate 125 μg twice daily for 3 weeks and once daily for a fourth week was delivered to infants who weighed between 500 and 1200 g. The dosage was doubled for infants who weighed ≥1200 g.**

Results. **Compared with placebo, treatment had no effect on either duration of supplemental O_2 therapy or ventilatory support as assessed by survival analysis. At 28 days, a trend toward a lower cortisol/creatinine ratio in the treatment group was noted compared with placebo (25.1 ± 18.9 vs 43 ± 14.4). In the fluticasone group at 28 days, the systolic arterial pressure (78 ± 3 vs 68 ± 3 mm Hg) and diastolic arterial pressure (43 ± 3.4 mm Hg vs 38 ± 2.0 mm Hg) were higher compared with baseline fluticasone values. The chest radiograph score was lower than baseline (2.8 ± 1.4 vs 3.7 ± 2.2) in the fluticasone group at 28 days. This study has a statistical power of 1.0 to detect a significant difference in the duration of oxygen supplementation of >21 days between the study groups.**

Conclusion. **We conclude that fluticasone propionate reduces neither supplemental O_2 use nor the need for ventilatory support in this patient population. However, fluticasone does have a positive radiologic effect in lowering chest radiograph scores. In addition, our data point to a possible association among inhaled fluticasone treatment and higher arterial blood pressure. Thus, the results of this investigation do not support the use of inhaled corticosteroids in the treatment of oxygen-dependent infants who have established moderate BPD.** *Pediatrics* **2005;115:e566–e572. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0951;** ***neonatal bronchopulmonary dysplasia, clinical trial, glucocorticoids, oxygen inhalation therapy.***

ABBREVIATIONS. BPD, bronchopulmonary dysplasia; F_{IO_2}, fraction of inspired oxygen.

Bronchopulmonary dysplasia (BPD) is an important sequela in the successful treatment of premature infants; BPD can occur without initial respiratory distress syndrome.[1] The development of BPD is strongly associated with respiratory distress syndrome, prematurity, low birth weight, male gender, and the presence of patent ductus arteriosus.[2] The pathophysiology of BPD is multifactorial; therefore, the treatment is multipronged.[3] At least 4 different mechanisms can explain abnormalities found in infants with BPD: (1) pulmonary edema, (2) bronchoconstriction and airway hyperactivity, (3) airway inflammation, and (4) chronic lung injury and repair. Inflammation is thought to be an important factor in the development of BPD.[4] Mechanical ventilation, oxygen use, and infection (either prenatally or postnatally acquired) are associated with an increase in the proinflammatory response of the immature lung.[5] Proinflammatory cytokines are present in the air spaces of ventilated preterm infants and in higher concentration in infants who subsequently develop BPD.[6] This inflammatory response, although possibly beneficial initially in favoring lung maturation,[5] is also associated with abnormal alveolarization—the process by which alveoli are formed during lung development.[7] Transgenic mice that overexpress proinflammatory cytokines have altered alveolarization.[8] Infants who die of BPD show fewer and larger alveoli than control subjects.[9] Thus, the inflammatory response that occurs in the lungs of these premature infants is possibly associated with abnormal lung maturation/development and BPD. Corticosteroids, particularly dexamethasone, have been used widely in an attempt to prevent or treat BPD by preventing or counteracting inflammation.[10] However, the clinical efficacy of corticosteroid inhalation in established BPD is not clear.

The hypothesis of this study is that steroid inhalation as a treatment for ongoing chronic inflammation, even after an initial course of systemic steroids, can reduce the length of oxygen supplementation in premature infants with established BPD. The objec-

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tive is to determine with a randomized, double-blind, controlled trial whether treatment of oxygen-dependent infants who have moderate BPD with inhaled fluticasone propionate permits earlier removal from oxygen therapy than does placebo administration within the 4-week treatment period. Some of the results of this study have been reported previously in abstract form.[11,12]

METHODS

Study Subjects

This study was a randomized, double blind, placebo-controlled, multicenter clinical trial approved by the institutional review boards of the 2 participating centers (Centre Hospitalier Universitaire de Québec, Quebec, Quebec, Canada, and Ste-Justine Hospital, Montreal, Quebec, Canada). Patients were enrolled between March 1997 and September 2000. Informed consent was obtained from the parents or legal guardians before inclusion. The study subjects were premature infants who were born at ≤32 weeks of gestation, had a postnatal age between 28 and 60 days, and had established BPD, as defined by O'Brodovich and Mellins.[1] Inclusion criteria consisted of oxygen requirement (fraction of inspired oxygen [F_{IO_2}]) ≥0.25 to maintain oxygen saturation between 88% and 92%, capillary or arterial blood partial pressure of carbon dioxide ≥45 mm Hg, chest radiograph compatible with BPD (as reviewed by an independent pediatric radiologist), and a hemoglobin level ≥110 g/L. Infants were excluded when there was evidence of sepsis or pneumonia (according to clinical diagnosis or positive blood, cerebrospinal fluid, or urine culture), persistent glucose intolerance (blood glucose ≥8.0 mmol/L), arterial hypertension (systolic blood pressure ≥95th percentile for age and weight[13]), renal failure (diuresis <1 mL/kg/hour for 24 hours and/or blood creatinine >100 mmol/L), systemic corticosteroid administration within 5 days before inclusion, change in diuretic dosage within 3 days before inclusion, or clinically significant congenital heart disease. Mechanically ventilated patients with oxygen requirements superior to F_{IO_2} >0.3 and nonintubated patients with oxygen requirements superior to F_{IO_2} >0.4 were also excluded. Before inclusion in the study, each infant was examined by the attending neonatologist and/or pediatric resident so as to rule out the presence of any acute disease. Urine output was measured for 24 hours before inclusion to ensure normal renal function. Oxygen supplements were noted on an hourly basis, and daily concentrations of O_2 were calculated as the mean of the concentration for 24 hours. The following assays were performed and measurements recorded at inclusion: vital signs, blood pressure, weight, body length, head circumference, complete blood count, chest radiograph, blood glucose, urinary cortisol, creatinine (24-hour collection), capillary blood gas, electrolytes, bound urea nitrogen, and blood creatinine. In the course of this study, the following assays were conducted and measurements were recorded: urinary Clinitest every 8 hours; blood pressure and weight daily; and weekly head circumference, body length, and capillary blood gas. Blood glucose was measured for positive Clinitest. A chest radiograph along with measurements of blood glucose, urinary cortisol and creatinine (24-hour collection), capillary blood gas, electrolytes, blood bound urea nitrogen, and blood plasma creatinine levels were repeated at the end of the study.

Study Protocol

Fluticasone propionate metered-dose inhalers (Flovent; GlaxoSmithKline, St-Laurent, Quebec, Canada; 125 μg of medication per activation) and placebo metered-dose inhalers, in identical format, were supplied by the drug manufacturer. These compounds were delivered through a valved spacing device of ~145-mL capacity (Aerochamber; Trudell Medical, London, Ontario, Canada) interposed between a neonatal anesthesia bag and the endotracheal tube of an infant patient or through a snug-fitting face mask. The delivery procedure was standardized with respect to ventilation technique and the activation procedure for the metered-dose inhaler. Infant stability was assessed first, and endotracheal suctioning was performed as necessary before medication delivery (endotracheal aspirations were not performed in the hour after drug administration except in urgent situations). Then, the metered-dose inhaler was shaken vigorously and inserted into the spacer. The spacer was attached to the neonatal anesthesia bag. The flow rate of fresh gas through the circuit was adjusted to the usual rate for the system using an F_{IO_2} value set at least 20% greater than the current value for an infant patient. The blow-off valve was adjusted to reach the appropriate pressure in the circuit. Then, the endotracheal tube was disconnected from the ventilator circuit and rapidly attached to the Aerochamber. The infant was manually ventilated with the neonatal anesthesia bag, and, as soon as adequate ventilation was established (as demonstrated by adequate chest rise), the fluticasone or placebo was administered 1 dose at a time. The metered-dose inhaler was activated at the end of expiration and 10 breaths were counted. A second dose was delivered to infants who received 250 μg, and then the infant was reconnected to the ventilator. For infants who were on continuous positive airway pressure via a nasopharyngeal endotracheal tube, the study drug was administered by the same procedure. For infants without ventilatory support, the technique was similar except that the Aerochamber was connected to a snug-fitting face mask. Fluticasone propionate was delivered at a dose of 125 μg twice daily for 3 weeks and once daily for a fourth and final week in infants who weighed between 500 and 1200 g. This dosage was doubled for infants who weighed ≥1200 g. The dosage chosen was based on the dosage used in childhood asthma cases seen in our institution at the initiation of this study. The resulting calculated dosage of 5 to 10 μg/kg of body weight (assuming lung deposition of 6%) was considered significant and probably sufficient for an effect to occur. Placebo was administered according to weight: 1 activation twice daily for 3 weeks and 1 activation daily for a fourth and final week for infants who weighed between 500 and 1200 g. The number of activations was doubled for infants who weighed ≥1200 g. Systemic corticosteroids were administered at the discretion of the attending physician. When systemic corticosteroids were used, inhaled therapy was discontinued, and the patient remained in the study solely for outcome measurement. Patients who presented acute respiratory deterioration associated with endotracheal intubation and an F_{IO_2} >0.35 were also removed from the study but were included in final outcome measures. An F_{IO_2} of 0.21 without any ventilatory support after 7 days was an indication to stop either fluticasone or placebo administration, as was sustained hyperglycemia (blood glucose ≥9 mmol/L and glucosuria >3 days), or when hypertension persisted for >3 days. Chest radiographs obtained at inclusion and at the end of the study were evaluated "blindly" by 2 radiologists and scored by consensus. The Edward scoring system was used for classification.[14] Nursing staff facilitated oxygen weaning. The administered oxygen concentration was adjusted to maintain a peripheral saturation of oxygen between 85% and 95% until it was lowered to room-air concentrations.

Randomization

Infants were assigned to either a placebo or a treatment group by block randomization. Fluticasone or placebo was contained within individually precoded metered-dose inhalers provided by GlaxoSmithKline. The pharmacist in charge of the medication, the treating physician, and the investigators all were unaware of treatment allocation. Infants were randomized at the coordinating center pharmacy. Intubated and extubated patients were stratified separately at randomization to ensure normal distribution of the severity of BPD within each group. Each block of 4 vials (1 for extubated and 1 for intubated patients) contained an equal number of placebo and fluticasone metered-dose inhalers to ensure normal distribution of the different treatment modalities.

Outcome Measures

The primary outcome measured was the mean difference in duration of oxygen supplementation among the treated and placebo groups. The difference in survival without supplemental oxygen at the end of the treatment period (28 days) was also assessed. Secondary outcomes included measuring effects on duration of ventilatory support, blood glucose, arterial pressure, diuresis, growth, cortisol axis, chest radiograph score, and length of hospital stay.

Safety Monitoring Board

Given that inhaled fluticasone propionate had not been studied previously in premature infants and owing to its off-label use in this investigation, the principal investigator (B.P.) could discon-

TABLE 1. Infant Characteristics in Fluticasone and Placebo Groups From Birth to Study Enrollment

Characteristic	Placebo ($N = 16$)	Fluticasone ($N = 16$)	P Value
Birth weight, g	926 ± 251	995 ± 439	.59
Gestational age, wk	27.2 ± 1.7	27 ± 2.3	.26
Male gender, %	11 (69)	12 (75)	.69
Multiple gestation, %	6 (37.5)	4 (25)	.45
Antenatal glucocorticoid exposure, %	12 (75)	11 (69)	.53
Ethnicity, %			
White	15 (94)	16 (100)	.31
Black	1 (6)	0	
Surfactant therapy, %	11 (69)	14 (88)	.10
Mechanical ventilation with endotracheal intubation, %	11 (69)	14 (88)	.19
Pneumothorax, %	0	1 (6)	.29
Perivascular interstitial emphysema, %	1 (6)	2 (13)	.54
Persistent fetal circulation, %	0	2 (13)	.14
Persistent ductus arteriosus, %	11 (69)	6 (38)	.08
Necrotizing enterocolitis, %	1 (6)	1 (12)	.37
Intraventricular hemorrhage, %	1 (6)	5 (31)	.07
Periventricular leukomalacia, %	2 (13)	1 (6)	.54
Retinopathy, %	5 (31)	7 (44)	.47
Hypotension, %	1 (6)	2 (13)	.37
Sepsis, %	2 (13)	2 (13)	1.0

tinue drug or placebo administration at his discretion in potential cases of severe adverse effects. Furthermore, an independent safety committee composed of a pharmacist and a neonatologist monitored and reviewed all cases. Members of this committee were not investigators of this study. The committee had full access to all protocols and data. Any member could stop the trial at any time if indicated.

Statistical Analysis

A retrospective patient chart review in our center (unpublished data, 1992) showed that infants with BPD received a mean course of 73 days of O_2 supplementation. Considering that only infants who were 28 days and older (with established BPD) are included in the current research project, a reduction in O_2 supplementation of 21 days was considered clinically significant. A calculated (statistical) minimal sample size of 30 patients was needed to demonstrate a reduction of oxygen supplementation of 21 days in the treated group using a 2-tailed level of significance of .05 and a power of 80%. Analysis was performed on an intent-to-treat basis on the 32 included patients. The study group baseline and outcome data were compared using the t test for continuous variables. A paired t test was applied to data from the baseline and final outcome groups. A χ^2 (Fisher's exact) test was used for categorical variables. Data are expressed as mean ± SD, unless stated otherwise. Survival curves and additional data analysis followed the Lifetest procedure of the SAS statistical program version 8.0 (SAS Institute, Cary, NC). Posthoc power calculations were conducted using Sample Power (SPSS, Chicago, IL). $P \leq .05$ was considered statistically significant. All statistical tests were 2 sided.

RESULTS

Thirty-two infants were included in this study. Three infants did not complete the study but were included in the analysis on an intent-to-treat basis. Treatment was discontinued in 2 infants in the placebo group at days 7 and 18 because of clinical pulmonary deterioration (both received open-label corticosteroids after withdrawal from the study) and in 1 infant from the placebo group on the second day of the protocol because of a central line–related sepsis. However, these patients were not included in the cortisol/creatinine analysis. One infant in the fluticasone group died from acute lung deterioration attributed to severe milk aspiration 2 months after completion of the study. Thus, 13 patients in the placebo group and 16 patients in the fluticasone group completed the study. The characteristics of the groups were similar before study entry (Table 1). The pulmonary-related characteristics at study enrollment were not statistically different among the groups (Table 2), with the exception of the mean daily fraction of oxygen use, which was significantly lower in the fluticasone group. As shown in Table 2, 10 patients in the placebo group received systemic dexamethasone ending at a median time of 18 days before enrollment (range: −47 to −15 days) and for a median duration of therapy of 3 days (range: 2–40 days). Twelve patients in the fluticasone group received systemic dexamethasone ending at a median time of 15 days before enrollment (range: −47 to −15 days) and for a median duration of therapy of 3 days (range: 2–17). In each study group, 5 of 16 infants received therapy by the endotracheal route while under mechanical ventilation (see Table 3; time to extubation). Treatment under continuous positive airway pressure via the nasopharyngeal tube was administered to 8 of 16 infants in the fluticasone group (including 2 previously intubated infants) and to 11 of 16 infants in the placebo group (including 4 previously intubated infants) for a respective mean duration of 14.4 ± 7.4 vs 13.1 ± 7.1 days ($P = .77$). Overall, 5 infants in the fluticasone group and 4 infants in the placebo group received the allocated treatment via face mask only.

Primary Outcomes

The results of the primary outcome are shown in Table 3 and Fig 1. Mean numbers of treated days are not different among the placebo and fluticasone groups (25 ± 9.0 vs 27 ± 7.5 days, respectively; $P = .49$). All patients who completed the study received the totality of the study drug, at the accurate dosage, without missing a dose as planned. As 3 infants who were withdrawn from the study were included in the analysis on an intent-to-treat basis and because 7 patients in the treatment group and 5 patients in the

TABLE 2. Pulmonary-Related Characteristics at Study Enrollment

Characteristic	Placebo (n = 16)	Fluticasone (n = 16)	P Value
Age at enrollment, d	45.4 ± 10	44.8 ± 11	.89
Mechanical ventilation with endotracheal intubation, %	5 (31)	5 (31)	1.0
Nasopharyngeal CPAP, %	4 (25)	3 (19)	.72
F_{IO_2}	0.30 ± 0.03	0.26 ± 0.03	.009
Prior postnatal dexamethasone, %	10 (63)	12 (75)	.53
Duration of dexamethasone, d, median (range)	3 (2–40)	3 (2–17)	—
Last day of dexamethasone dose before study day 0, d, median (range)	−18 (−47 to −15)	−15 (−45 to −10)	—
Previously inhaled corticosteroids, %	2 (12)	1 (6)	1.0
Duration of inhaled corticosteroid before study day 0	22 d and 3 d	20 d	—
Last day of inhaled corticosteroid dose before study day 0	Day −26 and −13	Day −18	—
Diuretics, %*	15 (94)	15 (94)	1.0
Caffeine, %*	16 (100)	16 (100)	1.0
Inhaled salbutamol, %*	4 (25)	4 (25)	1.0

CPAP indicates continuous positive airway pressure.
* Medications received during the full course of the study, some adjusted according to infant weight gain.

TABLE 3. Primary and Secondary Outcomes

Characteristic	Placebo (n = 16)	Fluticasone (n = 16)	P Value
Duration of treatment, study days*	25 ± 9.0	27 ± 7.5	.49
Study days with oxygen supplement*	19 ± 10.5	21 ± 7.9	.55
Total days with oxygen supplement, from birth to study end*	65 ± 14.2	67 ± 13.3	.65
Supplemental oxygen-free days, from birth to study end*	9 ± 11.7	9 ± 9.3	.48
Length of hospital stay, d*	132 ± 87	115 ± 69	.54
Time to extubation, d†	8 (2–44)	8 (4–12)	.35
Time to delivery from mechanical ventilation and/or CPAP from study entry, d*	15 ± 9.3	14 ± 7.9	.77

CPAP indicates continuous positive airway pressure.
* Mean ± SD.
† Median ± range, n = 5 in each group.

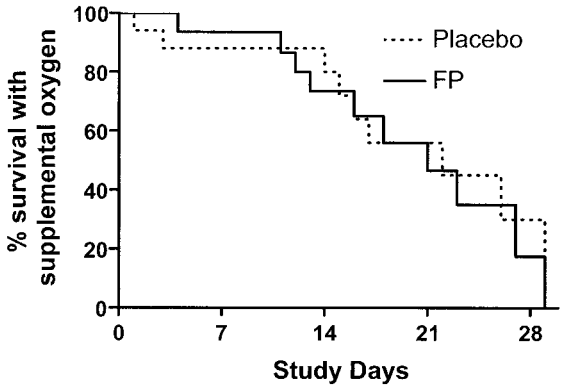

Fig 1. Survival with supplemental oxygen: Kaplan-Meier curves of survival for supplemental oxygen treatment until successful weaning to an F_{IO_2} (at 0.21) during the study period (28 days) among patients in the placebo group (n = 16; broken line) and fluticasone group (n = 16; straight line). The difference is not statistically significant (P = .76).

placebo group stopped receiving treatment before 28 days according to the protocol, days of duration of therapy do not add up to 28 days. There is no difference in the mean duration of oxygen supplementation among both study groups as shown in Table 3. Kaplan-Meier curves of survival after supplemental oxygen treatment until successful weaning (to a F_{IO_2} at 0.21) during the treatment period among patients in the placebo group (n = 16, broken line) and fluticasone group (n = 16, straight line) are not different statistically (P = .76).

Secondary Outcomes

Secondary outcomes are shown in Tables 3 and 4. Table 3 shows that, although slightly lower in the fluticasone group, the length of hospital stay did not differ ($P > .05$). Median time to extubation did not differ between both groups ($P > .05$). Table 4 shows that weight gain, body length, and head circumference were similar at baseline and at 28 days in both groups ($P < .05$). Arterial blood pressures (systolic and diastolic) were within normal limits at study entry, and values were comparable in both groups. Systolic blood pressure was significantly higher in the fluticasone group compared with baseline (78 ± 3.4 vs 68 ± 3.3 mm Hg, respectively; P = .04), as was the diastolic blood pressure (43 ± 3.4 vs 38 ± 2.0 mm Hg, respectively; P = .04). However, the observed differences were not significant when compared with placebo at 28 days (78 ± 3.4 vs 71 ± 2.5 mm Hg; P = .16). Blood glucose at entry and at 28 days was normal in both groups. Throughout the study, no patient showed any significant hyperglycemia. Urinary cortisol to creatinine ratios were comparable at baseline in both groups but were lower in the fluticasone group at 28 days (25.1 ± 18.9 mmol/L; n = 11) compared with study entry levels (49.8 ± 36.1 mmol/L; n = 11), although this was not statistically

TABLE 4. Baseline and 28-Day Physiologic Parameters of Studied Infants

Outcome Characteristic	Enrollment			28 d		
	Placebo	Fluticasone	*P* Value	Placebo	Fluticasone	*P* Value
Weight, g	1282 ± 421	1421 ± 732	.51	1944 ± 953	2029 ± 917	.77
Height, cm	39.0 ± 2.7	39.9 ± 5.2	.61	42 ± 3.7	42.3 ± 5.4	.88
Head circumference, cm	28.0 ± 2.1	27.6 ± 2.8	.70	31.1 ± 2.1	31.4 ± 3.8	.79
Blood glucose, mmol/L	4.8 ± 0.8	5.2 ± 0.6	.12	5.4 ± 1.1	5.6 ± 0.8	.56
Cortisol/creatinine ratio, nmol/mmol	52.6 ± 30.4	49.8 ± 36.1	.85	43 ± 14.4	25.1 ± 18.9*	.06
Arterial blood pressure						
Systolic, mm Hg	67 ± 3	68 ± 3.3	.83	71 ± 2.5	78 ± 3.4†	.16
Diastolic, mm Hg	37 ± 1.8	38 ± 2.0	.25	38 ± 3.0	43 ± 3.4‡	.21
Chest radiograph score	2.6 ± 1.5	3.7 ± 2.2	.15	2.8 ± 2.2	2.8 ± 1.4§	.50

* $P = .06$, fluticasone baseline vs 28 days, paired *t* test.
† $P = .04$, fluticasone baseline vs 28 days, paired *t* test.
‡ $P = .03$, fluticasone baseline vs 28 days, paired *t* test.
§ $P = .04$, fluticasone baseline vs 28 days, paired *t* test.

significant ($P = .06$). Again, the difference was not significant when compared with placebo at 28 days (43 ± 14.3 mmol/L; $P = .06$; $n = 10$). There was no carryover effect from previous dexamethasone therapy on the cortisol/creatinine ratio in either group (data not shown). The chest radiograph score was not statistically different in either the baseline or the 28-day groups, although a trend toward a higher score at baseline was noted in the fluticasone group compared with placebo. A significant reduction in the chest radiograph score was noted in the fluticasone group from baseline to 28 days (3.7 ± 2.2 vs 2.8 ± 1.4; $P = .04$).

DISCUSSION

In this study, we found no difference in the duration of oxygen use, ventilatory support, or the length of hospital stay in comparing inhaled fluticasone propionate treatment versus placebo administration in the population of premature infants with moderately severe, established BPD that we analyzed. However, we did find that fluticasone treatment is associated both with a higher systolic blood pressure at the end of therapy and with a lower chest radiograph score. We also report a trend toward lowering cortisol/creatinine ratios in the fluticasone-treated group.

Timing of therapy during the course of the disease may be an important factor to consider. Early patient treatment by fluticasone inhalation, before BPD onset, resulted in a higher rate of successful extubation at 14 days of postnatal age combined with an improvement in respiratory system compliance in ventilated preterm infants who had respiratory distress and were born at <32 weeks.[15] The number of intubated infants at the beginning of our study was insufficient to assess this endpoint. In agreement with our results, Fok et al[15] found no difference in oxygen dependence at 28 days, but they noted a trend toward reduced oxygen need at 36 weeks of postconceptional age. Moreover, a randomized, controlled study of inhaled fluticasone propionate in established oxygen-dependent infants who had BPD and were recruited at term (mean: 40 weeks' corrected gestational age) failed to show any significant effect on respiratory symptoms, oxygen supplementation, later oral corticosteroid use, or hospitalization rates after 1 year of therapy.[16] Our population was studied at an intermediate age between the groups examined by Fok et al[15] and Beresford et al.[16]

Although it is well known that inflammation is involved in the pathogenesis of BPD, it has yet to be shown that BPD is either preventable or treatable with either systemic or inhaled corticosteroids. An important number of patients in our study received either 1 or more courses of systemic dexamethasone before enrollment. Previous systemic corticosteroid exposure could have precluded any supplemental effect of later inhaled corticosteroid use. It is important to note that at the time we started the study, systemic steroids were used routinely in treating severe BPD cases in NICUs across North America.[17] Therefore, examination of a population with severe BPD (endotracheal intubation with an average F_{IO_2} >30%) was excluded from this study because at that time, placebo treatment was considered as potentially unethical.

The efficiency of the delivery system used potentially may have resulted in a lack of drug deposition and, thus, a lack of effect, although this is probably not the case. Using a rabbit model, O'Callaghan et al[18] showed a total of 6.4% deposition of beclomethasone (4.4% in trachea and main bronchus, given through a tracheostoma). These results were similar to other reports.[19] Compared with nebulization, a metered-dose inhaler coupled with an Aerochamber is more effective (10-fold increase) in lung drug deposition when used in conjunction with a neonatal ventilatory circuit.[20] Fok et al[15] demonstrated that fluticasone was delivered at least to the end of the endotracheal tube at a clinically significant dose. Moreover, the systemic effect of treatment observed at 28 days may suggest sufficient medication absorption.

Supporting evidence for a systemic effect of inhaled fluticasone, as measured by a significantly higher systolic blood pressure and a trend toward a lower urinary cortisol to creatinine ratio, was observed in our treated group. Other secondary outcome measures were not different between groups, except for the chest radiograph score. Cole et al[21] found a lower basal cortisol level in infants who received inhaled beclomethasone without evidence of adrenal suppression as reflected by the response

to a cosyntropin stimulation test. Fok et al[15] reported suppression of the basal and poststimulation plasma adrenocorticotropin hormone and cortisol concentrations in a group of infants who received fluticasone, compared with placebo. Although no clinically significant evidence of adrenal suppression was reported in our patient groups, we cannot exclude suppression of the hypothalamo-pituitary-adrenal axis, as it was not evaluated by stimulation testing. Moreover, one must be careful in extrapolating an isolated effect of fluticasone on the hypothalamo-pituitary-adrenal axis in this study because of the potential carryover effect of prestudy dexamethasone administration in a significant number of patients, even if not statistically significant. Blood pressure at the end of the study was higher than baseline in our treated group, which was not seen in the placebo group. Although not in the hypertensive range, it could reflect a systemic effect of inhaled corticosteroids on arterial systolic blood pressure. However, the association between fluticasone administration and higher blood pressure does not suggest a cause-and-effect relationship. To our knowledge, this is the first study to report a beneficial effect of inhaled fluticasone on radiologic appearance in this patient population. Although radiologic improvement is noted, it is unclear how this translates into clinical benefit.

The long-term effect of inhaled steroids on neurologic outcomes was not assessed in our population, the current sample size being inadequate to assess this type of multifactorial problem. As the population under study is mostly of French Canadian origin, the results could be different, although unlikely, if applied to a population with a differing genetic background.

The negative results of this study cannot be explained by a type II error (probability of not concluding that treatments differ when in reality they do). This study has a power of 1.0 to show a difference in oxygenation superior to 21 days between groups. In fact, this study is sufficiently powered to detect a difference in oxygenation of at least 9 days between groups with a β of .8 and an α of .05, had it been the case. To reach statistical significance for the observed difference of 2 days in oxygen supplementation between the groups, as found in this study (using an α error of .05 and a β error of .8), 636 infants would have to have been included in a hypothetical future trial. However, one should note that the "trend" for a shorter duration of oxygen supplement favors the placebo group.

CONCLUSIONS

This study shows that inhaled fluticasone propionate does not reduce the need for supplemental oxygen treatment in premature infants with moderate and established BPD. Data presented also suggest that both a radiologic improvement and a higher blood pressure level are possibly associated with inhaled corticosteroids in this population. In a recent joint statement, the American Academy of Pediatrics and the Canadian Pediatric Society concluded that the routine use of systemic dexamethasone is no longer recommended for treatment of infants with BPD. This is based on a lack of long-term benefits of dexamethasone and its association with an increased risk for short- and long-term complications, including impaired growth and neurodevelopmental delay.[10] Concerning inhaled corticosteroid therapy, these organizations stated that further clinical trials were required before future recommendations can be made.[10] The evidence of any clinically significant benefit of inhaled fluticasone or any other inhaled corticosteroids, other than earlier extubation, is scarce.[10] Our findings support these cautious recommendations. The 3 trials covering the spectrum of preventive therapy,[15] early established BPD, and late BPD[16] do not support fluticasone administration to this population of infants. Therefore, on the basis of this study, we cannot support the use of inhaled corticosteroids in the treatment of moderately severe BPD.

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