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Effects of Inhaled Beclomethasone Compared to Systemic Dexamethasone on Lung Inflammation in Preterm Infants at Risk of Chronic Lung Disease

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Summary. The purpose of this study was to compare the effects of daily inhaled beclomethasone (3 × 500 μg) started on day 3 of life, with that of systemic dexamethasone (0.5 mg/kg/day) started between days 11–13 on clinical variables, lung inflammation, and pulmonary microvascular permeability in preterm infants at risk for chronic lung disease (CLD). Following administration of surfactant, preterm neonates with RDS and a birth weight of less than 1,200 g were included in this comparative observational pilot study when still mechanically ventilated and with an oxygen requirement on the third day of life. The patients (gestational age 26.1 ± 0.9 weeks, birth weight 826 ± 140 g, mean ± SD) were alternately allocated to prophylactic treatment with inhaled beclomethasone (n = 7), or to early systemic dexamethasone therapy after day 10 of life, if clinically indicated (n = 9). Pulmonary inflammation and lung permeability were assessed by analyzing the levels of interleukin-8, elastase α_1 proteinase inhibitor, free elastase activity, and albumin in tracheal aspirates on days 10 and 14 of life. The secretory component of IgA served as reference protein.

We observed no significant differences in the concentrations of interleukin-8, elastase α_1 proteinase inhibitor, and albumin between the two groups on day 10 of life. On day 14, 3 (median; range, 1–3) days following initiation of dexamethasone treatment, concentrations of the inflammatory mediators and of albumin were significantly lower in the group on systemic steroid therapy than in the group treated with inhaled steroids ($P < 0.01$). Additionally, there was a significant difference in oxygen requirements between both groups on day 14. In the group treated with inhaled steroids, concentrations of the inflammatory mediators, albumin, and oxygen requirements did not show a difference between day 10 and 14.

We conclude that, in contrast to systemic dexamethasone treatment, a 12-day course of inhaled beclomethasone does not affect lung inflammation and pulmonary microvascular permeability in preterm infants at risk for CLD within the first 2 weeks of life. **Pediatr Pulmonol. 1999; 27:383–387.**

Key words: dexamethasone; inhaled corticosteroids; lung inflammation; bronchopulmonary dysplasia; chronic lung disease of newborns.

INTRODUCTION

Systemic therapy with corticosteroids is often used in ventilated preterm infants when early signs of chronic lung disease are present. A few days after initiation of treatment, the drug facilitates extubation in most infants. The mode of action is not clear as yet. Besides other possible mechanisms,[1] the observed clinical effect may be due to a downregulation of pulmonary inflammation and a reduction of lung microvascular permeability.[2–4] While systemic dexamethasone has a high potential for side effects,[5,6] topical application of corticosteroids might diminish these adverse effects. However, the value of inhaled steroids in the prevention or treatment of CLD has not yet been clearly demonstrated. In the present observational study, we compared the effect of inhaled beclomethasone, initiated at day 3 of life, with that of systemic dexamethasone, started between day 11–13 on clinical variables and on lung inflammation in preterm infants at risk for CLD (birth weight <1,200 g). Pulmonary inflammation and lung permeability were assessed by analyzing the levels of inflammatory mediators and

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albumin in tracheal aspirates. We hypothesized that a 12-day course of treatment with inhaled beclomethasone, started on day 3 of life, would lead to a reduction of pulmonary inflammation and microvascular permeability comparable to that observed following 1–3 days of systemic dexamethasone therapy.

METHODS

Drug Administration Protocol

Preterm neonates with a birth weight <1,200 g were included in the study while they were still mechanically ventilated and had an oxygen requirement ($FiO_2 \geq 0.3$) on the third day of life. During a 5-month period, 30 infants with birth weights <1,200 g were consecutively admitted to the neonatal intensive care units of the Children's Hospital in Cologne, and the Perinatal Center at Women's Hospital, Cologne-Holweide. Three neonates died within the first 3 days of life. Of the remaining 27 infants, 5 did not receive mechanical ventilation, 3 were extubated within 3 days after birth, and 3 ventilated infants did not have an oxygen requirement of 30% or more on day 3 of life. Sixteen patients entered the study, and were alternately allocated to treatment with inhaled beclomethasone or systemic dexamethasone. Systemic dexamethasone was the standard treatment of early chronic lung disease in our institution whenever extubation was not possible within the first 10 days of life, and if the infant had an oxygen requirement with an $FiO_2 \geq 0.3$. Due to the poor clinical results (CLD in 6 of 7 patients), allocation to inhaled steroids was stopped for ethical reasons after treatment of 7 neonates. Thus, 7 of 16 patients were treated with inhaled steroids, and 9 patients received systemic steroids. Inhaled beclomethasone (Sanasthmax, Glaxo, Bad Oldesloe, Germany) was given from day 3–28 of life. It was administered by an Aerochamber (Trudell Medical, London, Ontario, Canada) into the ventilatory circuit at a dose of 3 × 2 puffs of 250 μg (= 1.5 mg/day). This system has been shown to deliver reproducible quantities of drug to the lower respiratory tract.[7,8] After extubation, inhalation therapy was continued by face mask, and the Aerochamber was connected to a ventilation bag. No systemic steroids were given to infants treated with inhaled steroids during the first month of life. However, systemic dexamethasone was given thereafter if the infant was still on mechanical ventilation. Systemic dexamethasone was given at a starting dose of 0.5 mg/kg/day for 3 days; thereafter, the dose was gradually tapered over 10 or 28 days, according to the clinical status of the infant. Duration of treatment was at the discretion of the attending physician. There were no differences between both treatment groups regarding birth weight (inhaled steroids: 800 g (500–1,020), systemic steroids: 847 g (660–1,030), mean (range); gestational age (26.1 (25–28) vs. 26.2 (25–28)) , male/female ratio (3/4 vs. 3/6); prenatal treatment with steroids (5 vs. 7); history of prenatal maternal infection (2 vs. 4); airway colonization with Ureaplasma urealyticum at birth (total cultures, 13/16; positive cultures, 3/13; 1/6 vs. 2/7); and maximum oxygenation index on day 1 (9.5 (5.6–19.6) vs. 10.5 (5.3–16.0)).

The diagnosis of respiratory distress syndrome (RDS) was based on a typical chest radiograph, oxygen dependency, and clinical signs of respiratory distress. Patients with RDS were treated with natural surfactant.[9] Arterial oxygen saturation (SaO_2) was continuously recorded, and supplemental oxygen was administered to keep SaO_2 values between 90–95%. All neonates received intravenous indomethacin for prophylactic treatment of patent ductus arteriosus (PDA) on the first day of life. Before initiation of indomethacin therapy, ductus-dependend cardiac malformations had been ruled out by Doppler and two-dimensional echocardiography. A second course of indomethacin treatment was performed in one patient of both groups in whom reopening of PDA occurred. Chronic lung disease of the newborn (CLD) was defined by oxygen dependency and radiological abnormalities on day 28.[10] The study was approved by the hospital ethics committee, and informed parental consent was obtained.

Sampling of Tracheal Aspirates, and Assays of Inflammatory Mediators, Albumin, and Secretory Component

The sampling of tracheal aspirates and the assays of interleukin-8, elastase α_1 proteinase inhibitor, free elastase activity, albumin, and the secretory component (SC) for IgA were performed as recently described.[11] To avoid errors due to the sampling procedure, concentrations of the inflammatory mediators and albumin were related to concentrations of the secretory component of IgA as the reference protein (mediator/SC ratio).

Statistical Analysis

On day 14, the biochemical and clinical data were compared between the systemic dexamethasone treatment group (post-treatment, 1–3 days after initiation of therapy) and the inhaled beclomethasone treatment group (post-treatment, 12 day days after initiation of therapy) using the Mann-Whitney U test. Data between days 10–14 of life within each group were compared using the Wilcoxon signed rank test. $P < 0.05$ was considered sta-

Abbreviations

CLD	Chronic lung disease
FiO_2	Fraction of inhaled oxygen
PDA	Patent ductus arteriosus
RDS	Respiratory distress syndrome
SaO_2	Arterial oxygen saturation
SC	Secretory component

TABLE 1—Concentrations of Elastase α_1-Proteinase Inhibitor, and Numbers of Patients With Detectable Free Elastase in Tracheal Aspirate Fluid in the Groups of Neonates Treated With Inhaled Beclomethasone (Started on Day 3) and Systemic Dexamethasone (Started on Day 11–13)[1]

Mediator	Treatment	Day 10	Day 14
Eα_1-PI (ng/μgSC)[2]	Beclomethasone	111 (9–211)	94 (48–130)
	Dexamethasone	79 (22–112)	12 (4–45)*,**
Elastase[3]	Beclomethasone	1/7	3/7
	Dexamethasone	1/9	0/9

[1]Values are expressed as median, with ranges from minimum to maximum.
[2]Elastase α_1-proteinase inhibitor.
[3]No. of patients with free elastase activity/total numbers of patients.
*$P < 0.01$, before vs. after dexamethasone.
**$P < 0.01$, beclomethasone group compared to dexamethasone group.

tistically significant. As some of the data were not normally distributed, values were expressed as medians (25th–75th percentile). Demographic and clinical outcome data were expressed as mean ± SD; differences were analyzed by t-test.

RESULTS

Inflammatory Mediators in Tracheobronchial Aspirate Fluid and Oxygen Requirements

Concentrations of interleukin-8, elastase α_1 proteinase inhibitor, free elastase, and albumin in tracheobronchial aspirate fluid are shown in Table 1 and Figure 1.

There were no significant differences in the concentrations of interleukin-8, elastase α_1 proteinase inhibitor and albumin between the two groups on day 10 of life. On day 14, 3 (median; range, 1–3) days following initiation of dexamethasone treatment, concentrations of the inflammatory mediators and of albumin were significantly lower in the group treated with systemic steroid therapy than in the group treated with inhaled steroids ($P < 0.01$). Additionally, there was a significant difference in oxygen requirements between the two groups on day 14 (FiO_2 inhaled vs. systemic steroid group, day 10: 0.33 ± 0.07 vs. 0.38 ± 0.06, n.s.; day 14: 0.38 ± 0.06 vs. 0.23 ± 0.02, $P < 0.05$). Concentrations of the inflammatory mediators, showed no difference, but albumin and oxygen requirements slightly increased between days 10–14 in the group treated with inhaled steroids. In contrast, all variables decreased significantly in the group treated with systemic dexamethasone.

Outcome Data

Patients treated with inhaled beclomethasone spent more days on mechanical ventilation and in supplemental oxygen compared to dexamethasone-treated neonates (Table 2). Additionally, development of CLD was more common in the group treated with inhaled beclomethasone. There was one late death beyond day 28 due to necrotizing enterocolitis in an infant belonging to the group treated with inhaled beclomethasone. The overall frequency of CLD in all infants surviving for more than 28 days was 8/27 (29.6%).

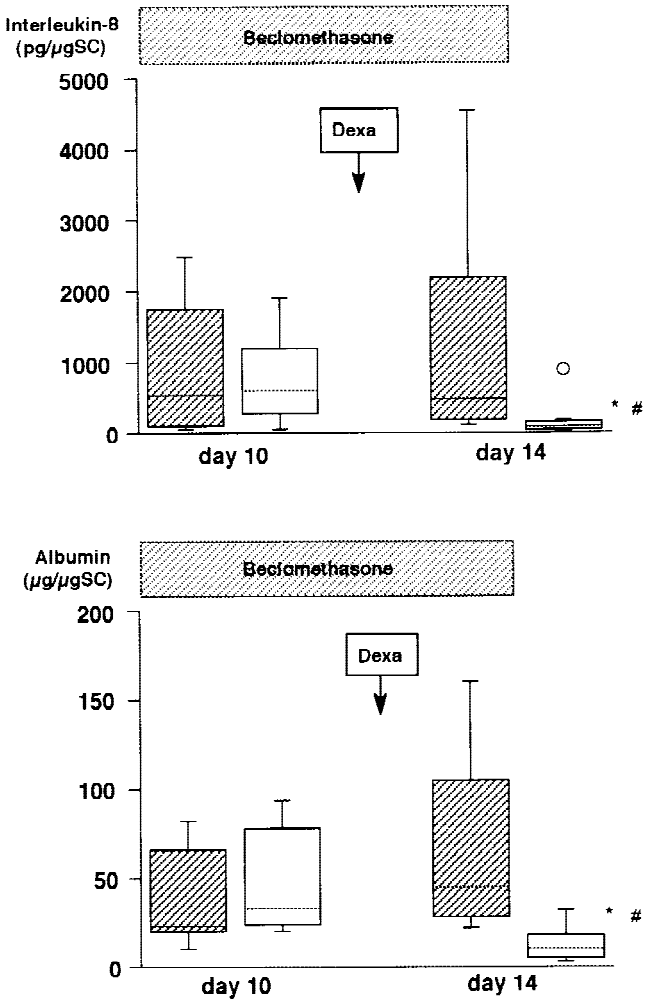

Fig. 1. Concentrations of interleukin-8 (top) and albumin (bottom) in tracheal secretions of ventilated preterm infants treated with inhaled beclomethasone, started on day 3 of life (hatched bars), or with systemic dexamethasone, started between day 11–13 of life (open bars). Initiation of systemic treatment is indicated by arrow. Concentrations of interleukin-8 and albumin are adjusted to concentrations of the secretory component of IgA (SC). Bars indicate medians (25th–75th percentile). *$P < 0.01$, systemic dexamethasone vs. inhaled beclomethasone on day 14. #$P < 0.01$, before (day 10) vs. after (day 14) dexamethasone.

DISCUSSION

In this small observational pilot study we found that, in contrast to systemic dexamethasone treatment, a 12-day

TABLE 2—Outcome Data of Patients

	Beclomethasone inhalation (n = 7)	Systemic dexamethasone (n = 9)
Days on mechanical ventilation[1]	21.0 ± 7.0	15.2 ± 1.2*
Days on supplemental oxygen[1]	38.2 ± 11.8	22.7 ± 11.5*
CLD	6	2

[1]Data are presented as mean ± SD.
*$P < 0.05$.

course of inhaled beclomethasone did not affect lung inflammation and pulmonary microvascular permeability in preterm infants at risk for CLD. The experience with inhaled steroids in premature infants with CLD is limited. Although therapeutic trials in selected patients started as early as 1989,[12] most reports are abstracts, with few patients treated,[13–17] and there are only three randomized, placebo-controlled studies evaluating the effect of inhaled steroids in ventilated preterm infants within the first month of life.[18–20] It has been shown that inhaled steroids exert some effect on pulmonary function during long-term treatment in ventilated preterm infants. However, the onset of this effect is delayed.[18] Compared to placebo, inhaled beclomethasone facilitated extubation in ventilator dependent neonates more than 2 weeks of age.[19] In preterm infants with mild oxygen dependency treated at a median age of 4 weeks, there was a marked difference in the speed of action of systemic compared to inhaled steroids. A significant effect of systemic dexamethasone on gas exchange and lung mechanics was observed 36 h following initiation of treatment. Inhaled steroids showed an effect on these variables only after 1 week of treatment.[21] In our study, pulmonary function was not evaluated. However, on day 14 oxygen requirements were markedly lower in infants on systemic dexamethasone therapy compared to patients treated with inhaled steroids. This difference persisted until day 28.

Systemic dexamethasone treatment significantly decreased lung microvascular permeability in preterm infants at risk for CLD.[2–4] There is evidence that this effect was, at least in part, due to a downregulation of pulmonary inflammation, as the concentrations of inflammatory mediators in tracheal aspirate fluid were decreased.[4,22,23] The effects of systemic dexamethasone treatment on inflammatory indicators and microvascular permeability in tracheobronchial aspirate fluid found in the present study are in agreement with the results of other investigators.[2,3,22] Only one study has investigated the effect of inhaled steroids on lung inflammation.[20] Although some improvement of gas exchange variables was noted, the authors found that 7 days of treatment with inhaled budesonide had no effect on total or differential cell counts in bronchoalveolar lavage fluid compared to controls. Concentrations of inflammatory mediators in tracheal secretions of preterm infants following treatment with inhaled steroids have not been investigated so far. The results of this pilot study indicate that, in contrast to systemic treatment, topical application of the drug does not affect lung microvascular permeability and concentrations of inflammatory mediators. A possible explanation could be that the dose of steroids reaching the alveoli may be too low. It has been shown in experimental settings that following administration of beclomethasone via an Aerochamber, only 1–3% of the dose was detectable in the lungs.[8,24] Although we treated our infants with a large dose of beclomethasone (1,500 μg/day), only 45 μg is likely to have reached the lung parenchyma, the site of the predominant lesion in CLD. Additionally, important target cells might not be reached by the inhaled route. If lung inflammation is an important cause of increased pulmonary vascular permeability in CLD, the alveolar cells are not the only cells affected, but the endothelial and interstitial cells are also damaged. If this is the case, the intravascular route may be the more effective route for an adequate therapeutic or prophylactic effect in early CLD. Favorable results of inhaled steroids on lung function have been reported in infants with established CLD at age 3–24 months.[25–27] At this late stage of the disease, bronchial inflammation may contribute more to the clinical symptoms than during the very early phase, i.e., the first 2 weeks of life.

In conclusion, this study shows that a 12-day course of prophylactic inhaled steroids did not affect lung inflammation and pulmonary microvascular permeability in preterm infants at risk for CLD. The role of inhaled steroid in the prevention or therapy of CLD remains to be defined. Our data do not support a preventive effect of treatment with inhaled beclomethasone in the early course of the disease. However, larger studies are necessary to compare the effects of inhaled steroids and systemic dexamethasone on the development of CLD.

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