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Methylprednisolone, an alternative to dexamethasone in very premature infants at risk of chronic lung disease

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Abstract *Objective:* To evaluate the benefits and the medium-term side effects of methylprednisolone in very preterm infants at risk of chronic lung disease.

Study design: Forty-five consecutive preterm infants (<30 weeks' gestation) at risk of chronic lung disease were treated at a mean postnatal age of 16 days with a tapering course of methylprednisolone. The outcome of treatment was assessed by comparison with 45 consecutive historical cases of infants treated with dexamethasone; the infants did not differ in baseline characteristics.

Results: There were no differences between groups in the rate of survivors without chronic lung disease. Infants treated with methylprednisolone had a higher rate of body weight gain during the treatment period (median 120 g, range 0 to 190, vs. 70 g, range –110 to 210, $P = 0.01$) and between birth and the age of 40 weeks (median 1660 g,

range 1170–2520, vs. 1580 g, range 1040 to 2120, $P = 0.02$). The incidence of both glucose intolerance requiring insulin (0 % vs. 18 %, $P = 0.006$) and cystic periventricular leukomalacia (2 % vs. 18 %, $P = 0.03$) was lower among methylprednisolone-treated infants.

Conclusion: Our observations confirm methylprednisolone to be as effective as dexamethasone and to have fewer side effects. A randomized control trial is needed to further study the efficacy and safety of methylprednisolone in very premature infants at risk of chronic lung disease.

Key words Respiratory distress syndrome · Chronic lung disease · Methylprednisolone · Dexamethasone · Infant, premature, diseases · Bronchopulmonary dysplasia · Leukomalacia, periventricular

Introduction

Despite continuous progress in neonatal intensive care, bronchopulmonary dysplasia remains an important concern in extremely premature infants. Dexamethasone, commonly administered for the treatment of bronchopulmonary dysplasia and the prevention of chronic lung disease, contributes to decreased oxygen requirement and to faster extubation [1, 2, 3, 4, 5, 6, 7, 8, 9]. Although long-term benefits on the respiratory status are less well documented, some recent studies suggest that

prophylactic administration of dexamethasone decreases the incidence of chronic lung disease [2, 5, 6, 7, 8]. However, several adverse effects of this therapy have been reported, including glucose intolerance, increased risk of nosocomial infection, gastroduodenal bleeding, and occurrence of a catabolic state with retarded weight gain [9, 10]. Some of these complications are more frequent when treatment is initiated very early after birth [8, 10]. Whether dexamethasone administration may be associated with an increased rate of retinopathy of prematurity remains controversial.

Concerns about potential adverse effects of dexamethasone on neurodevelopmental outcome have arisen in 1997 [11]. Since then several studies have reported an increased incidence of neuromotor abnormalities or cerebral palsy in infants treated early with dexamethasone [12, 13]. As a result the alarming but preliminary report by Yeh et al. [11] we initiated a pilot study in 1997 with methylprednisolone in very premature infants at high risk of chronic lung disease. Compared to dexamethasone, methylprednisolone – another glucocorticoid with a shorter half-life and a negligible mineralocorticoid effect – has a lower anti-inflammatory activity. This glucocorticoid has been safely used in various clinical conditions such as status asthmaticus refractory to other types of treatment [14, 15], unresolving acute respiratory distress syndrome [16], and acute graft rejection [17]. Over a 14-month period 45 consecutive very premature infants were prospectively followed in our institution to compare the efficacy and potential short-term adverse effects of methylprednisolone with a historical group of infants treated with dexamethasone during the preceding 15 months.

Methods

Subjects and treatment protocols

During a 14-month period (November 1997 to December 1998) a series of all 45 consecutive cases of very preterm infants (gestational age ranging from 24 to 29 weeks) at risk of chronic lung disease were treated with a tapering course of methylprednisolone hemisuccinate (Solu-medrol, Pharmacia & Upjohn) in doses given intravenously every 6 h (0.6, 0.4, 0.2 mg/kg per dose for 3 days each). This 9-day course is equivalent to a total dose of 72 mg hydrocortisone [18]. The accompanying diluent for the vials of Solu-

medrol does not contain benzyl alcohol. After this 9-day course the corticoid treatment was prolonged with betamethasone (Celestone, Shering-Plough) on alternate days for a total of 21 days at the orally administered dose of 0.1 mg/kg. All ventilated infants with a FIO_2 requirement of 0.30 or more beyond the first week of life were considered for steroid therapy. Nonventilated infants on continuous positive airway pressure were treated with the aim of avoiding reintubation only if there were apparent signs of respiratory failure, including hypercarbia and progressive increase in FIO_2 above 0.30.

The control group consisted of all the 45 consecutive very preterm infants who were treated with dexamethasone phosphate (Soludecadron, Merck Sharp & Dohme-Chibret) over the period from July 1996 to October 1997. During this period the recommended regimen was a 9-day tapering course of dexamethasone (equivalent to a total dose of 76 mg hydrocortisone) in doses given intravenously twice a day (0.25, 0.125, 0.1 mg/kg per dose for 3 days each), followed by betamethasone on alternate days for a total of 21 days at the orally administered dose of 0.1 mg/kg. Indications for steroid therapy were identical over the two time periods in our institution.

There were no differences in the baseline characteristics of the two groups regarding gestational age, birthweight, rate of small for gestational age infants, sex, exposure to antenatal steroids, mode of delivery, or reason for preterm delivery (Table 1). There were no significant differences in rates of surfactant administration, air leak, or patent ductus arteriosus requiring treatment between the two groups. By the time that steroid treatment was started, oxygen requirements were similar in the two groups. The steroid treatment was initiated at a median age of 16 days in the methylprednisolone group and 15 days in the dexamethasone group. During the two time periods full enteral feeding was reached at a similar mean postnatal age, and calorie or protein intakes did not differ significantly during the treatment period (Table 2). There was no significant difference between groups in the total dose of systemic steroid administered (expressed in milligrams of hydrocortisone equivalent; Table 3).

Table 1 Antenatal and postnatal baseline characteristics in methylprednisolone- and dexamethasone-treated infants (*PDA* patent ductus arteriosus, *CPAP* continuous positive airway pressure)

	Methylprednisolone (<i>n</i> = 45)	Dexamethasone (<i>n</i> = 45)	<i>P</i>
Gestational age (weeks) ^a	26.9 (24.0–29.6)	26.7 (24.1–29.7)	0.7
Birth weight (g) ^a	780 (480–1230)	820 (500–1440)	0.2
Less than 26 weeks	10 (22 %)	10 (22 %)	1
Inborn	40 (89 %)	38 (84 %)	0.5
Antenatal steroids	39 (87 %)	36 (80 %)	0.4
Prolonged rupture of membranes	9 (20 %)	8 (18 %)	0.8
Chorioamnionitis	12 (27 %)	15 (33 %)	0.5
Small for gestational age	8 (18 %)	5 (11 %)	0.4
Cesarean section	30 (67 %)	27 (60 %)	0.5
Male sex	22 (49 %)	23 (51 %)	0.8
Surfactant administration	43 (96 %)	40 (89 %)	0.2
Pulmonary air leak	7 (16 %)	7 (16 %)	1
PDA requiring indomethacin	27 (60 %)	26 (58 %)	0.8
PDA requiring surgical ligation	7 (16 %)	10 (22 %)	0.4
Infants on nasal CPAP at first steroid administration	11 (24 %)	7 (16 %)	0.3
Age at first steroid administration (days) ^a	16 (8–70)	15 (7–28)	0.7
Median FIO_2 at first steroid administration ^a	0.4 (0.3–0.7)	0.4 (0.3–0.9)	0.8

^a Median (range)

Table 2 Calorie intake (kcal/kg per day) in methylprednisolone- and dexamethasone-treated infants

	Methylprednisolone	Dexamethasone	<i>P</i>
Day 0	116 ± 24	115 ± 24	0.8
Day 3	126 ± 21	126 ± 18	0.9
Day 6	135 ± 17	134 ± 18	0.9
Day 15	132 ± 16	137 ± 13	0.13

Outcome variables

Pulmonary outcome variables included the median time to assisted ventilation independence, the rate of reintubation (reintubation required for surgical procedure was not taken in account), the incidence of chronic lung disease (defined as the need for either ventilatory support or supplemental oxygen at 36 weeks of gestational age), death before discharge from the hospital, and the length of hospital stay. Parameters measured were the rate of change in body weight, the rate of glucose intolerance as measured by the need for insulin therapy (indicated when blood glucose concentration was ≥ 16.7 mmol/l in three consecutive measurements over a 24-h period associated with 4+ of glycosuria on Labstix), and any of the following diagnoses: nosocomial infection ascertained by the association of positive blood cultures with serum C-reactive protein concentration of more than 20 mg/l (normal < 10), necrotizing enterocolitis, upper gastrointestinal bleeding, stages 3 or 4 retinopathy of prematurity, and cystic periventricular leukomalacia. This latter was defined as localized or extensive echolucent areas observed on cranial ultrasonography performed weekly until 36 weeks of gestational age.

Statistical analysis

Categorical variables were compared by either the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were compared with Student's *t* test or the Wilcoxon rank sum test. All statistical

tests were two-tailed. Statistical significance was set at $P < 0.05$ for all analyses.

Results

Five infants in the methylprednisolone group died: one from congenital cytomegalovirus infection, one from septic shock, and three from respiratory failure. Five infants in the dexamethasone group died: one from respiratory failure and four from extensive cystic periventricular leukomalacia.

There were no differences between groups in the pulmonary outcome variables (Table 3). Extubation was unsuccessful for five infants of the methylprednisolone group and seven of the dexamethasone group. These infants eventually received a second steroid course.

There was a significant difference in bodyweight gain between the two groups. Infants treated with methylprednisolone had a higher rate of body weight gain during the treatment period than infants treated with dexamethasone (median 120 g, range 0 to 190, vs. 70 g, range -110 to 210, $P = 0.01$; Table 2). At 40 weeks of age methylprednisolone-treated infants had a higher gain in body weight (median 1660 g, range 1170 to 2520 vs. 1580 g, range 1040 to 2120, $P = 0.02$). There were fewer infants with glucose intolerance requiring insulin or cystic periventricular leukomalacia in the methylprednisolone group (Table 2). In seven of the eight infants with cystic periventricular leukomalacia in the dexamethasone group, ultrasound scans were normal before the initiation of treatment, and the echolucent areas appeared 1–2 weeks after the beginning of therapy. There was no difference in the incidence of gastroin-

Table 3 Outcomes and side effects in methylprednisolone- and dexamethasone-treated infants

	Methylprednisolone	Dexamethasone	<i>P</i>
Delay between treatment initiation and extubation (days) ^a	9 (3–35)	8 (2–80)	0.8
Extubation within 10 days after treatment initiation	19/30 (63 %)	20/36 (56 %)	0.5
Reintubation after extubation	5/30 (17 %)	7/35 (20 %)	0.7
Death	5/45 (11 %)	5/45 (11 %)	1
Chronic lung disease among survivors at 36 weeks	23/40 (58 %)	25/42 (60 %)	0.9
Survivors without chronic lung disease	18/45 (40 %)	16/45 (36 %)	0.7
Length of hospital stay (days) ^{a,b}	109 (64–197)	100 (62–365)	0.7
Total dose of hydrocortisone equivalent (mg) ^a	91 (42–471)	87 (47–297)	0.7
Gain in body weight over the 9-day course (g) ^a	120 (0–190)	70 (-110–210)	0.01
Weight at full-term (g) ^{a,b}	2530 (1830–3500)	2450 (2100–3240)	0.08
Gain in body weight from birth to term (g) ^{a,b}	1660 (1170–2520)	1580 (1040–2120)	0.02
Necrotizing enterocolitis	0/45 (0 %)	1/45 (2 %)	–
Gastrointestinal bleeding	0/45 (0 %)	0/45 (0 %)	–
Retinopathy of prematurity grade 3 or 4	1/45 (2 %)	0/45 (0 %)	–
Nosocomial infections after treatment initiation	2/45 (4 %)	6/45 (13 %)	0.3
Required insulin therapy after treatment initiation	0/45 (0 %)	8/45 (18 %)	0.006
Cystic periventricular leukomalacia	1/45 (2 %)	8/45 (18 %)	0.03

^aMedian (range)

^bAmong survivors

testinal bleeding, nosocomial infection, necrotizing enterocolitis, or severe retinopathy of prematurity between groups.

Discussion

Methylprednisolone has been found to be clinically effective in both children and adults with steroid-responsive inflammatory diseases [14, 15, 16, 17]. Dexamethasone is the only synthetic glucocorticoid used for over more than 20 years in the treatment of very premature infants with (or at risk of developing) bronchopulmonary dysplasia. Whether methylprednisolone – a synthetic glucocorticoid different from dexamethasone in many aspects including chemical structure, metabolism, and affinity for the steroid receptor – is clinically effective in immature infants is unknown. We therefore carried out a preliminary study to assess the efficacy of methylprednisolone in very premature infants at high risk of chronic lung disease. This efficacy was compared to that of dexamethasone in a historical control group. Short-term effects on respiratory status and on rates of survivors without chronic lung disease did not differ between the two groups. The effectiveness of methylprednisolone in our study was also similar to that of dexamethasone as reported in the literature. For instance, in a recent randomized trial comparing two dexamethasone regimens, the median time to extubation was 10 days and the incidence of chronic lung disease in survivors was 66% [8]. In our study there was a higher rate of body weight gain in the methylprednisolone group than in the dexamethasone group during the treatment period, and the number of infants requiring insulin was lower. A short-term negative effect of dexamethasone on gain in body weight has previously been reported [8]. A long-term effect on growth has also been observed in the Collaborative Dexamethasone Trial [3]. However, because there was no untreated group in our study, it cannot be excluded that methylprednisolone also has a negative effect on body growth, although this effect appears less pronounced than that of dexamethasone.

The incidence of cystic periventricular leukomalacia was higher in infants treated with dexamethasone than in those treated with methylprednisolone. Caution must be used in drawing conclusions from our data regarding this major outcome. Cystic periventricular leukomalacia is a rare complication, and the present study involved only a small number of infants. Nevertheless, chorioamnionitis and prolonged rupture of membranes, two high antenatal risk factors for periventricular leukomalacia, were not less frequent in the methylprednisolone group. Two recent studies suggest that neuromotor dysfunction and cerebral palsy are more frequent in infants treated with prophylactic dexamethasone compared to placebo [12, 13]. O'Shea and colleagues [13] have also shown that dexamethasone recipients have a higher risk of developing major intracranial abnormalities detected by ultrasonography. In addition, an important increase in the rate of cystic periventricular leukomalacia among preterm infants treated very early with dexamethasone has been observed in a retrospective study with historical controls [19]. A preliminary report from a recent prospective randomized trial also suggests that the incidence of periventricular leukomalacia is higher among infants treated with dexamethasone [20]. In several countries including France the preparation of dexamethasone, but not that of methylprednisolone, contains sulfite. That the increased incidence of periventricular leukomalacia observed with the early administration of dexamethasone may be explained by the presence of sulfiting agents in the preparation cannot be excluded. Sulfiting agents, commonly used as preservatives in parenteral emergency drugs, has been shown to be neurotoxic *ex vivo*, especially in combination with peroxynitrite [21, 22].

The major limitation of this study was the use of a historical comparison group. Although treatment methods for respiratory distress syndrome including antenatal glucocorticoid exposure, surfactant substitution, mechanical ventilation, and other subordinate measures were not modified over this short period of time, it cannot be excluded that more subtle changes occurred. This pilot study emphasizes the potential benefits of methylprednisolone, but a further randomized and controlled trial is warranted.

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