Lipid Intolerance in Neonates Receiving Dexamethasone for Bronchopulmonary Dysplasia

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Background: We hypothesized that dexamethasone induces hypertriglyceridemia (triglyceride levels >2.82 mmol/L [250 mg/dL]) and increases free fatty acid (FFA) levels and that steroid-induced hypertriglyceridemia is associated with hyperinsulinemia and elevated FFA levels.

Objective: To study the effect of dexamethasone sodium phosphate on lipid metabolism in neonates receiving intravenous lipids.

Design: A prospective cohort study with patients serving as their own controls.

Setting: Neonatal Intensive Care Unit, Children’s Hospital at Strong, Rochester, NY.

Methods: All neonates younger than 29 weeks’ gestational age at birth receiving 3 g/kg per day of intravenous lipids who were to start dexamethasone therapy for bronchopulmonary dysplasia were eligible. Exclusion criteria included neonates with active infection, prior hypertriglyceridemia, bleeding manifestations, recent surgery, thyroid medication, and human recombinant insulin intravenous infusion therapy. Ten neonates were studied. Blood was drawn for triglyceride, FFA, and insulin assays before initiating and at 1, 2, 3, and 5 days after starting dexamethasone therapy. On day 3, dexamethasone dosage was decreased as per protocol. Intravenous lipid intake was kept constant. Statistical analysis was done using a paired t test.

Results: Six of 10 neonates reached a state of hypertriglyceridemia (95% confidence interval, 26.2%-87.8%). The mean average increase in triglycerides, insulin, and FFA levels in neonates receiving 3 g/kg per day of intravenous lipids after initiation of dexamethasone therapy was 0.75 mmol/L (66.6 mg/dL) ($P = .007$), 127 pmol/L ($P = .006$), and 47.5 µmol/L ($P = .65$), respectively. Six neonates who developed hypertriglyceridemia had significantly elevated mean peak FFA levels (918.3 µmol/L) prior to developing hypertriglyceridemia compared with 4 neonates (mean peak FFA levels, 380.2 µmol/L) who had triglyceride levels lower than 2.82 mmol/L (250 mg/dL) ($P = .002$).

Conclusion: We conclude that dexamethasone induces hypertriglyceridemia in the presence of hyperinsulinemia and increased FFA levels.


Editor’s Note: At this point, we can only guess at the long-term consequences of this double whammy therapy for very low-birthweight infants.

Catherine D. DeAngelis, MD

Most premature neonates need intravenous (IV) lipids during the first few weeks of life to acquire adequate energy intake and prevent essential fatty acid deficiency before they can tolerate all nutrition via enteral feeds.$^1$ Lipid intolerance has been described in infants who are extremely premature, small for gestational age, or who have an active infection.$^2$ Elevated lipid concentrations have been associated with a deterioration of pulmonary function,$^7$ impairment of neutrophil function,$^8$ and displacement of bilirubin from albumin binding sites, with an increased risk for kernicterus.$^{10,11}$

Bronchopulmonary dysplasia (BPD) is the most common form of chronic lung disease in neonates. Dexamethasone, a synthetic corticosteroid, has been used for the prevention and treatment of BPD.$^{12,13}$ However, administering dexamethasone therapy to neonates is not benign and is associated with multiple side effects, including poor weight gain.$^{14,15}$ Administering dexamethasone therapy to premature infants may cause an impairment in glu-
SUBJECTS, MATERIALS, AND METHODS

STUDY DESIGN

The cohort study was prospective with patients serving as their own controls. The study was reviewed and approved by the University of Rochester Medical Center Research Subjects Review Board, Rochester, NY. For the purpose of the study, hypertriglyceridemia was defined as triglyceride values equal to or higher than 2.82 mmol/L (250 mg/dL).

INCLUSION CRITERIA

All premature neonates 24 to 29 weeks’ gestational age at birth admitted to the Children’s Hospital at Strong, Neonatal Intensive Care Unit, Rochester, who were selected to receive a long course (>7 days) of dexamethasone therapy for BPD and who were receiving 3 g/kg per day of IV lipids were considered eligible for this study. The diagnosis of BPD was determined by the clinical staff based on findings from chest radiographs and increasing fraction of inspired oxygen requirements. Gestational age was determined by obstetric history or, if obstetric history was unreliable, by Ballard examination. Dexamethasone therapy was administered at the discretion of the attending neonatologist. Eligible patients were enrolled in the study following parental consent.

EXCLUSION CRITERIA

Exclusion criteria included known genetic disorders; active infections treated with antibiotics; triglyceride levels equal to or higher than 2.82 mmol/L (250 mg/dL); thyroid problems requiring medications; surgery performed within 72 hours of study enrollment; bleeding manifestations or abnormal findings on a coagulation profile, which precluded the routine use of heparin sulfate in IV fluids; and/or patients requiring an epinephrine IV infusion or insulin drip.

METHODS

Patients receiving 3 g/kg per day of IV lipids (Liposyn II; Abbott Laboratories, Abbott Park, Ill) who were to start dexamethasone therapy for BPD were identified 24 to 48 hours before dexamethasone therapy was initiated. Parental consent was obtained if the research subjects did not meet the exclusion criteria. Baseline values for triglyceride, FFA, and insulin levels were measured 1 to 2 hours before initiating dexamethasone therapy. Baseline values were measured after patients had been receiving 3 g/kg per day of IV lipids for at least 2 consecutive days. Dosage for dexamethasone therapy followed the protocol of Avery et al, which included 0.25 mg/kg every 12 hours for the first 6 doses, followed by 0.15 mg/kg every 12 hours for the next 6 doses. The IV lipids were continued at 3 g/kg per day and were infused continuously at the same hourly rate. At 1, 2, 3, and 5 days following initiation of dexamethasone therapy, blood was drawn at the same time of day to measure the triglyceride, FFA, and insulin levels. The same source of blood was used for the whole study period for individual patients because FFA levels differ between arterial and venous blood. Blood specimens were immediately centrifuged and serum was separated. Serum was kept frozen at -40°C until analysis. Free fatty acid levels were measured using an enzymatic analysis (Amyl Chemicals USA, Inc, Richmond, Va); insulin levels were measured using a radiometric method (Ortho Clinical Diagnostics, Raritan, NJ). Both FFA and insulin levels were measured in duplicate, and the mean values were considered for statistical analysis. The mean coefficient of variations for duplicate measurements of each sample for insulin and FFA levels were 3% and 1%, respectively.

During the study period (1) heparin intake was kept constant and infused continuously; (2) no treatment with new medications, such as insulin, epinephrine, bronchodilators, or diuretics, was initiated; and (3) lipid intake was kept constant, unless hypertriglyceridemia developed. If triglyceride levels were 2.82 mmol/L to 4.52 mmol/L (250-400 mg/dL), IV lipid intake was decreased to 1 g/kg per day. If triglyceride levels continued to increase, even when the patient was receiving 1 g/kg of IV lipids per day, IV lipid intake was decreased to 0.5 g/kg per day. However, if triglyceride levels decreased when the patient was receiving 1 g/kg per day, IV lipid intake was continued at 1 g/kg per day. If the patient was receiving 0.5 g/kg per day of IV lipids and triglyceride levels increased, IV lipid intake was discontinued. At any time, if triglyceride levels were higher than 4.52 mmol/L (400 mg/dL), IV lipid administration was discontinued.

STATISTICAL ANALYSIS

The paired t test was used to test the null hypothesis that the mean changes in average serum levels of triglycerides, FFA, and insulin while the patient is receiving 3 g/kg per day of IV lipids and triglyceride levels increased, IV lipid intake was discontinued. The mean coefficient of variations for duplicate measurements of each sample for insulin and FFA levels were 3% and 1%, respectively. The mean coefficient of variations for duplicate measurements of each sample for insulin and FFA levels were 3% and 1%, respectively.

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Based on the animal data and our experience from this retrospective analysis, we hypothesized that dexamethasone induces hypertriglyceridemia and increases FFA levels and that steroid-induced hypertriglyceridemia is associated with hyperinsulinemia and elevated FFA levels.

Ten neonates were enrolled in the study. Two neonates could not complete the fifth day of the study: one because insulin therapy was initiated for hyperglycemia (blood glucose level >10.0 mmol/L [180 mg/dL]); another because not enough blood was available to analyze the insulin levels. The mean postmenstrual age of all study patients at the time of enrollment was 289/7 weeks, with a mean chronological age of 17.3 days. The mean postmenstrual age for the group of neonates with triglyceride levels lower than 2.82 mmol/L (250 mg/dL) (n = 4) was 29/7 weeks. The mean postmenstrual age for the group of neonates who developed hypertriglyceridemia (n = 6) was 28/7 weeks. Six of 10 research subjects were female. Nine of 10 neonates had an appropriate size for gestational age. Only 1 infant was small for gestational age; however, the triglyceride levels for this patient are shown in Figure 2.

Intake rates for IV lipids, glucose, energy, and heparin did not change between baseline (prior to start of dexamethasone therapy) and the time of peak values of triglyceride levels after initiating dexamethasone therapy, as given in the Table.

The mean serum triglyceride, insulin, and FFA levels at baseline (0 hour) and 1, 2, 3, and 5 days after initiation of dexamethasone therapy are shown in Figure 1. The mean average increase in triglyceride, insulin, and FFA levels for patients receiving 3 g/kg of IV lipids per day after initiation of dexamethasone therapy was 0.75 mmol/L (66.6 mg/dL) (P = .007), 127 pmol/L (P = .006), and 47.5 µmol/L (P = .65), respectively.

Daily individual serum triglyceride levels for each patient are shown in Figure 2. Six (60%) of 10 research subjects developed hypertriglyceridemia. Even those neonates with triglyceride levels lower than 2.82 mmol/L (250 mg/dL) had higher triglyceride levels after starting dexamethasone therapy. All 6 neonates with hypertriglyceridemia required a decrease in IV lipid intake according to the protocol outlined in the “Methods” subsection of the “Subjects, Materials, and Methods” section. In 3 of 6 neonates with hypertriglyceridemia, triglyceride levels decreased as the IV lipid intake was decreased because of hypertriglyceridemia. However, in 3 other neonates with hypertriglyceridemia, triglyceride levels decreased only after day 3 when the dexamethasone dosage was decreased. The triglyceride levels also decreased with the decrease in dexamethasone dosage in 2 of 3 neonates with triglyceride levels lower than 2.82 mmol/L (250 mg/dL).

Daily serum insulin levels for individual patients are shown in Figure 3. Nine of 10 neonates had an increase in insulin levels after starting dexamethasone therapy. All 6 neonates with hypertriglyceridemia had elevated insulin levels (mean peak insulin level, 342 pmol/L) while receiving dexamethasone therapy. Four neonates were female. Nine of 10 neonates were an appropriate size for gestational age. Only 1 infant was small for gestational age; however, the triglyceride levels for this patient are shown in Figure 2 of the “Methods” subsection of the “Subjects, Materials, and Methods” section. In 3 of 6 neonates with hypertriglyceridemia, triglyceride levels decreased as the IV lipid intake was decreased because of hypertriglyceridemia. However, in 3 other neonates with hypertriglyceridemia, triglyceride levels decreased only after day 3 when the dexamethasone dosage was decreased. The triglyceride levels also decreased with the decrease in dexamethasone dosage in 2 of 3 neonates with triglyceride levels lower than 2.82 mmol/L (250 mg/dL).

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Figure 1. Serum triglyceride, insulin, and free fatty acid levels (mean ± SD) at baseline (0 hour) and 1, 2, 3, and 5 days after initiation of dexamethasone sodium phosphate therapy for the research subjects. Triglyceride and insulin levels were significantly elevated in neonates undergoing dexamethasone therapy.

Table

<table>
<thead>
<tr>
<th>Comparisons of Heparin, Energy, Lipid, and Glucose at Baseline and After Initiation of Dexamethasone Therapy*</th>
<th>At Baseline†</th>
<th>After Initiation of Dexamethasone Sodium Phosphate Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin sulfate intake, U/kg per day</td>
<td>0.13 ± 0.0</td>
<td>0.13 ± 0.01</td>
</tr>
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<td>Energy intake, J/kg per day</td>
<td>6.7 ± 6.8</td>
<td>4.1 ± 4.1</td>
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<td>Lipid infusion rate, g/kg per hour</td>
<td>9.9 ± 2.0</td>
<td>8.9 ± 2.3</td>
</tr>
<tr>
<td>Glucose intake, mg/kg per minute</td>
<td>20.0 ± 2.8</td>
<td>16.0 ± 1.8</td>
</tr>
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*All values are given as mean ± SD.
†Patients receiving 3 g/kg of lipids per day, intravenously.
with triglyceride levels lower than 2.82 mmol/L (250 mg/dL) also had elevated insulin levels (mean peak insulin level, 404 pmol/L). There was no difference between the insulin levels in the neonates who developed hypertriglyceridemia and the neonates with triglyceride levels lower than 2.82 mmol/L (250 mg/dL) \( (P = .69) \). The insulin levels peaked 1 day prior to or concomitantly to the peak in triglyceride levels. Insulin levels in 5 of 6 neonates with hypertriglyceridemia decreased concomitantly with the decrease in dexamethasone dosage or the decrease in IV lipid intake. One neonate who had persistent hyperinsulinemia, despite a decrease in dexamethasone dosage and IV lipid intake, also had persistent hypertriglyceridemia. In 3 neonates with triglyceride levels lower than 2.82 mmol/L (250 mg/dL), the insulin levels decreased with the decrease in dexamethasone dosage.

Daily serum FFA levels for individual patients are shown in Figure 4. The FFA levels increased in 7 of 10 neonates after starting dexamethasone therapy. Two neonates had high baseline FFA levels (mean baseline FFA value, 1020.2 µmol/L) compared with 8 other neonates (mean baseline FFA value, 334.5 µmol/L). If these 2 neonates are not accounted for, the mean average FFA values (678.2 µmol/L) for neonates receiving 3 g/kg of IV lipids per day after initiation of dexamethasone therapy are significantly elevated above the baseline FFA values (334.5 µmol/L), \( P = .02 \). All 6 neonates with hypertriglyceridemia had elevated FFA levels after starting dexamethasone therapy. Mean peak FFA values for 6 neonates with hypertriglyceridemia and 4 neonates with triglyceride levels lower than 2.82 mmol/L (250 mg/dL) were 918.5 µmol/L and 404.5 µmol/L, respectively. The FFA levels were significantly higher in neonates with hypertriglyceridemia than in neonates with triglyceride levels lower than 2.82 mmol/L (250 mg/dL) \( (P < .004) \). As with triglyceride and insulin levels, the FFA levels decreased concomitantly with the decrease in dexamethasone dosage or IV lipid intake.

**COMMENT**

Premature infants with BPD have high energy requirements to sustain postnatal weight gain, and IV lipids are an important energy source for them. Infants with BPD who are treated with dexamethasone have poor weight gain.14,15 Treatment with dexamethasone impairs not only glucose but protein metabolism in premature infants.14,16 From this review we have demonstrated that infants with BPD who receive both IV lipids and dexamethasone also have altered lipid metabolism.

Triglycerides, the major component of lipid emulsions, are hydrolyzed by lipoprotein lipase into FFA and glycerol. Heparin releases the lipase from the capillary endothelium.12 The fatty acids bound to albumin are transferred to various tissues, mainly adipose and liver, where they are oxidized to provide energy or are reesterified and stored as triglycerides. An infant’s ability to use lipids as an energy source depends on appropriate enzyme activity in the liver and adipose cells to metabolize the FFA.
In premature infants, about 30% of energy is derived from the β-oxidation of fatty acids.1,3,5 Numerous factors have been associated with hyperlipidemia in neonates.2,6 Diminished tolerance to IV lipids has been described in infants who are extremely premature.7 As these infants mature, triglyceride levels usually fall with the increase in lipoprotein lipase activity.3,33 The rate of lipid infusion also affects serum concentrations of triglycerides and FFAs; the maximum recommended lipid infusion rate is less than 0.25 g/kg per hour.35,36 Lipid metabolism may also be altered during the immediate postoperative period,37 and by administering an epinephrine drip,38 thyroid medications,39 or glucose.40 Numerous animal studies have demonstrated that steroid use is also associated with hypertriglyceridemia.17-24 The inductive effect of steroids on triglyceride synthesis in the liver is affected by the presence of insulin.22 Insulin increases triglyceride synthesis in the liver. Steroids induce hyperinsulinemia by 2 separate mechanisms. (1) Steroids have a pronounced pancreatic effect, causing a rise in insulin levels.29 (2) In addition, steroids inhibit glucose uptake into cells and decrease glucokinase activity, thereby causing hyperglycemia. In response to hyperglycemia, more insulin is secreted, causing hyperinsulinemia.29 In our study, 9 of 10 neonates had increased insulin levels after starting dexamethasone therapy, 4-fold above baseline values. There was no difference in glucose intake between the baseline and peak values, which could have caused hyperinsulinemia. De novo fatty acid synthesis is required for synthesis of triglycerides.31 Dexamethasone increases the activity of acetyl-CoA carboxylase, a rate-limiting enzyme for de novo fatty acid synthesis.22 This effect is not seen in the absence of insulin, suggesting that insulin has a permissive action in increasing the activity of acetyl-CoA carboxylase.22 In our study we found patients whose insulin levels peaked 1 day prior to or concomitantly with the peak in triglyceride levels, suggesting that insulin levels were high for this permissive action on de novo fatty acid synthesis. In the presence of dexamethasone and insulin, instead of being oxidized for energy production, most of the fatty acids synthesized are reesterified to form triglycerides.31,41,42 Though insulin increases triglyceride synthesis in liver, its effect on triglyceride secretion has been demonstrated to be biphasic.19 Short-term hyperinsulinemia (<24 hours) decreases triglyceride secretion; however, neonates with hyperinsulinemia for longer than 24 hours lose this inhibitory effect, and secretion of triglycerides increases.18,19 All of the neonates in our study had hyperinsulinemia for longer than 24 hours; however, only 6 neonates developed hypertriglyceridemia. All 4 neonates who did not develop hypertriglyceridemia in the presence of hyperinsulinemia also had significantly lower FFA levels compared with neonates who developed hypertriglyceridemia. Our findings suggest that not all patients with hyperinsulinemia develop hypertriglyceridemia and substrate availability is a significant factor. Insulin levels decreased with the decrease in dexamethasone dosage or IV lipid intake except in 1 neonate. This particular neonate also continued to have hypertriglyceridemia, despite decreases in dexamethasone dosage and IV lipid intake.

Dexamethasone increases triglyceride synthesis and secretion in the liver.17-24 Steroid use also causes hypertriglyceridemia by decreasing the activity of lipoprotein lipase, which hydrolyzes triglycerides into FFA and glycerol.43 However, Cole et al21 demonstrated in an animal model that augmented synthesis and secretion of triglycerides largely contribute to steroid-induced hypertriglyceridemia. With dexamethasone therapy, we found the incidence of hypertriglyceridemia to be 60% with a 2-fold increase in serum triglyceride levels. A much higher triglyceride level could have been observed if the lipid intake had not been decreased because of hypertriglyceridemia. Hypertriglyceridemia improved with a decrease in dexamethasone dosage or IV lipid intake or both.

Free fatty acid (substrate) availability also affects triglyceride synthesis.25-27 Steroids are catabolic and cause fatty acid mobilization from adipose tissue. Insulin decreases fatty acid mobilization at the adipose tissue level and is an antagonist to the steroid effect. Though 7 of 10 neonates had an increase in FFA levels after starting dexamethasone therapy, mean average FFA levels for neonates receiving 3 g/kg of IV lipids per day were not significantly elevated above the baseline levels. These may be related to the high baseline FFA levels found in 2 neonates. We do not have an explanation for these high baseline FFA levels. Neonates with hypertriglyceridemia had higher FFA levels than neonates with triglyceride levels lower than 2.82 mmol/L (250 mg/dL). Our findings support the findings of others who found that elevated FFA levels are associated with the development of hypertriglyceridemia.25-27 In addition, fatty acids are potent antagonists of the action of insulin to decrease triglyceride secretion.23 The lower FFA levels in neonates with triglyceride levels lower than 2.82 mmol/L (250 mg/dL) may be related to the slightly higher insulin levels in these neonates compared with neonates who developed hypertriglyceridemia.

In summary, dexamethasone induces hypertriglyceridemia that occurs in the presence of hyperinsulinemia and elevated levels of FFAs. Because of concomitant hyperinsulinemia, we speculate that dexamethasone therapy is associated with decreased fatty acid oxidation. This may partially explain why neonates undergoing dexamethasone therapy have poor weight gain. Neonates receiving IV lipids and dexamethasone therapy should be closely monitored for hypertriglyceridemia and increased FFA levels, especially if there is a risk for bilirubin encephalopathy.

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