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Effect of Dexamethasone Treatment on Serum GH, IGF-I, and the Binding Proteins IGFBP-1 and -3 in Ventilated Very Preterm Infants

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ABSTRACT

Very preterm infants developing bronchopulmonary dysplasia frequently show a compromised growth in the neonatal period especially when steroids are given to facilitate weaning from the ventilator. The aim of this study was to evaluate the short-term effect of dexamethasone (DEXA) on the GH-IGF axis in ventilated very preterm infants developing bronchopulmonary dysplasia. We studied 10 very preterm artificially ventilated infants with bronchopulmonary dysplasia [median (range) gestational age 27.5 wk (25.9–32.0 wk), median (range) birth weight 970 g (610–2150 g)] immediately before and 2 d after the start of DEXA treatment. On both days of study, serum GH profiles were obtained, and serum IGF-I and IGF binding protein (IGFBP) -1 and -3 levels were measured. The ventilation score and the nutritional intake were calculated. Before the start of DEXA treatment, the median serum mean GH level was 12.0 μg/L (6–28.4 μg/L), whereas 2 d after the start of DEXA treatment the median serum mean GH level declined significantly to a value of 4.4 μg/L (1.7–11.9 μg/L). During DEXA treatment, mean, baseline, and maximal GH levels (Pulsar analysis) were significantly lower compared with pretreatment levels ($p < 0.01$, $p < 0.01$, and $p < 0.05$, respectively). Serum IGF-I and IGFBP-3 levels did not decline during DEXA. Serum IGFBP-1 levels were significantly lower compared with pretreatment levels ($p < 0.01$). Serum GH levels during DEXA treatment were correlated with neither the time interval between the administration of DEXA and the second GH profile nor the cumulative DEXA dose administered. Ventilation score and nutritional intake did not significantly correlate with serum GH, IGF-I, or IGFBP-1 or -3 levels, either before or after the start of DEXA. Two days of DEXA treatment in very preterm ventilated infants has a suppressive effect on serum GH levels, without an acute decline in serum IGF-I levels. A concomitant decrease in serum IGFBP-1 levels was found. **(*Pediatr Res* 54: 37–43, 2003)**

Abbreviations

DEXA, dexamethasone
BPD, bronchopulmonary dysplasia
IGFBP-1, IGF-binding protein-1
IGFBP-3, IGF-binding protein-3

Very preterm infants developing BPD, with a persistent need for artificial ventilation and oxygenation, frequently show a very compromised growth in the neonatal period (1, 2). Their growth will be further attenuated when DEXA treatment is given after conservative treatment, including increased ventilation settings and fluid restriction, has failed to wean them from the ventilator (3–5). The hormonal mechanisms underlying this early postnatal growth retardation and the role of glucocorticosteroids have not been elucidated. DEXA has a catabolic effect by increasing protein breakdown and alters skeletal metabolism by inhibition of intestinal calcium absorption, stimulation of renal calcium excretion, and suppression of collagen turnover in preterm infants (6–8).

Glucocorticosteroids have been suggested to have a suppressive effect on the pituitary GH secretion with attenuation of the spontaneous GH secretion and decreased GH responses to various stimuli (9–11). A direct antagonizing effect of DEXA on the epiphyseal cartilage to the action of GH has been reported, probably by inhibition of the local secretion and paracrine action of IGF-I and the inhibition of the expression of the GH and IGF-I receptor (12).

The clinical significance of GH in the perinatal period is not well understood, although GH-deficient infants show a reduction in birth length, suggesting some role for GH in regulation of fetal growth (13). In the postnatal period in particular,

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insulin and IGF-I are important regulators of physical growth, and in mice disruption of genes for IGF-I, IGF-II, or their receptors results in intrauterine growth retardation (14–16).

So far, no studies have evaluated the short-term effect of DEXA treatment on serum GH levels and growth factors in ventilated very preterm infants. To understand the effect of DEXA on spontaneous GH secretion and the GH-IGF axis, we performed a 6-h GH profile and measured serum IGF-I and IGFBPs, before and 2 d after the start of DEXA treatment in very preterm infants with BPD.

METHODS

Patients. Preterm infants born with a gestational age ≤ 32 wk, developing BPD, were included in the study if the attending neonatologist decided to start DEXA treatment to wean the infant from the ventilator. The indication to start DEXA treatment was a persistent need for artificial ventilation and oxygen dependency after 1 wk of age when conservative treatment such as increased ventilation settings, fluid restriction, diuretics, antibiotics, and inhalation therapy had failed to wean the infant from the ventilator. DEXA treatment was started with a dosage of 0.5 mg/kg per day, in two doses per day, during 3 d. Thereafter the dosage was tapered to 0.3 mg/kg per day for 3 d, and gradually tapered every 3 d to 0.1 mg/kg per day every other day during a 3-wk period. Infants were excluded if they had a persistent ductus arteriosus, pulmonary infection, sepsis, grade 3 or 4 intraventricular hemorrhage, chromosomal defects, or major congenital anomalies or when the mother was being treated for an endocrine disorder with GH, thyroxin, or thyreostatic drugs during pregnancy. All patients were admitted to the neonatal intensive care unit of the Sophia Children's Hospital in Rotterdam, The Netherlands.

The Medical Ethics Committee of the Erasmus University Medical Center approved the protocol, and written informed consent was obtained from the parents of each child.

Methods. All patients had an indwelling arterial catheter and were studied twice. Immediately before the start of DEXA treatment and 2 d thereafter plasma samples were taken every 30 min during a 6-h period for determination of serum GH levels and once to determine serum IGF-I, IGFBP-1, and IGFBP-3 levels. Sampling of blood in these very preterm infants was restricted because of the small size of the infants and their severe illness. The total blood volume of these infants is 50–80 mL, and it was unacceptable to withdraw more than 5% of the total blood volume for study purposes. A longer period or more frequent sampling was therefore impossible. All blood samples were stored directly on ice for no longer than 3 h. After centrifugation, plasma samples were frozen (−20°C) until assayed.

Birth weight was expressed in SD scores according to Usher and McLean (17). Daily weights were obtained by the nursing staff using an electronic weight scale (Digital Baby Scale, model DS-30 A; Kubota, Ltd, Japan).

The attending neonatologist provided routine care and feeding decisions. According to the policy of the neonatal intensive care unit, infants were started on parenteral nutrition on the second day of life, and enteral feedings were initiated on d 7. All infants were continuously fed, and blood glucose levels were determined every day. Preterm infant formulas were used with a caloric density of 80–88 kcal/100 mL and a protein content of 2.4–2.6 g/100 mL. On both days of study, the protein, energy, and fat intakes were calculated. The severity of respiratory failure was assessed by calculating the ventilation score (mean airway pressure times inspired fraction of oxygen).

Hormonal assays. All hormonal determinations were performed in the Endocrine Laboratory of the University Hospital Rotterdam, The Netherlands.

GH levels in plasma were measured using a two-site immunoradiometric assay (ELSA-HGH; CIS bio international, ORIS Group, France). The assay measured the 22-kD GH and showed no cross-reactivity with 20-kD GH. All samples were analyzed in duplicate in the same assay. The WHO First International Reference Preparation WHO 80/505 was used as a standard. The intraassay and interassay coefficients of variation were < 2.8% and 4.4%, respectively. The detection limit of the assay was 0.04 μg/L.

Serum IGF-I levels were determined by RIA (SM-C-RIA-CT, Biosource Europe SA), after acid-ethanol extraction (18). The sensitivity was 0.25 ± 0.10 ng/mL, the intraassay and interassay coefficients of variation were < 6.1% and 9.9%, respectively. Cross-reactivity with IGF-II was 0.2%, with insulin, < 0.001%, and with GH, < 0.01%.

Serum IGFBP-1 levels were determined using a two-site immunoradiometric assay (Total IGFBP-1 IRMA DSL-7800; Diagnostic Systems Laboratories, Webster, TX, U.S.A.). The sensitivity of the assay was 0.33 ng/mL, and the intraassay and interassay coefficients of variation were < 5.2% and 6.0%, respectively. No cross-reactivity was seen with serum IGFBP-2, -3, -4, -5, and -6.

Serum IGFBP-3 levels were determined using a two-site immunoradiometric assay (IGF-BP3 IRMA, DSL-6600; Diagnostic Systems Laboratories). The sensitivity of the assay was 0.5 ng/mL, with intraassay and interassay coefficients of variation of < 3.9% and 1.9%, respectively.

Analysis of GH profiles. The GH profiles were analyzed with the Pulsar program developed by Merriam and Wachter (19) and adapted for Quick Basic by Rosberg and Albertsson-Wikland (PC-Pulsar, 1987). From the Pulsar analysis the following values were extracted: the overall mean, baseline, and maximal GH levels.

Statistical analysis. Statistical analysis was performed using SPSS 9.0 for Windows 95, SPSS software (Chicago, IL, U.S.A.). All hormone levels were logarithmically transformed in the analyses. Differences between paired samples were tested with the Wilcoxon signed ranks test. Correlations were evaluated with the nonparametric Spearman's rank correlation. Results are expressed as the median (range), unless indicated otherwise. Two tailed p values ≤ 0.05 were considered significant.

RESULTS

Clinical characteristics. Ten very preterm infants, seven boys and three girls, with a median (range) gestational age of

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27.5 wk (25.9–32.0 wk) and a median (range) birth weight of 970g (610–2150 g), were included in the study. Six infants were treated with antenatal steroids.

The clinical characteristics of the infants on both days of study, before and 2 d after start of DEXA treatment, are shown in Table 1. The infants were studied when they had received at least three doses of DEXA. The nutritional intake was not significantly different between both days of study. Three infants were receiving parenteral nutrition. The ventilation score, however, had decreased significantly on the second day of study compared with the day before the start of DEXA ($p < 0.05$).

GH profiles. The GH profiles of the individual patients before and during DEXA treatment are shown in Figure 1. Mean pretreatment serum GH levels varied between 6 and 28.4 μg/L with a median of 12.0 μg/L, whereas 2 d after the start of DEXA treatment the mean GH level had declined to a median of 4.4 μg/L. Two days after the start of DEXA treatment the overall mean, baseline, and maximal serum GH levels were significantly lower compared with pretreatment levels ($p < 0.01$, $p < 0.01$, and $p < 0.05$, respectively; Table 2). In all patients, except one, the GH levels declined during DEXA treatment. The percentage decline in serum mean GH levels was 54%, in serum baseline GH levels 56%, and in serum maximal GH levels 35%, and not correlated with gestational or postnatal age.

Serum GH levels were not significantly different between patients receiving parenteral or enteral nutrition. The time interval between the administration of DEXA and the start of the second GH profile varied. In the first five patients DEXA was administered between 6 and 0 h before the start of the second profile, whereas in the other five patients DEXA was also given during the sampling period. No significant correlation was found between the time interval between administration of DEXA and the serum GH levels during the second profile.

The cumulative dose of DEXA (in milligrams per kilogram of body weight) administered before the second GH profile did not correlate with mean, baseline, and maximal GH levels, nor with the percentage decline in serum GH levels. The same applied for the number of DEXA doses given before the second profile.

IGF-I and IGFBP-1 and -3 levels. During DEXA treatment, serum IGFBP-1 levels significantly declined from a median of 69.9 to 13.5 ng/mL ($p < 0.01$), whereas serum IGF-I and IGFBP-3 levels did not change (Fig. 2). The number of doses of DEXA administered before the start of the second profile did not significantly correlate with serum levels of IGF-I, IGFBP-1, and IGFBP-3. The cumulative dosage of DEXA (in milligrams per kilogram of body weight) given before the start of the second profile showed a trend toward lower IGF-I levels, although this did not reach significance ($r = -0.6$; $p = 0.08$). Serum IFG-I, IGFBP-1, and IGFBP-3 levels were not significantly different between patients receiving parenteral or enteral nutrition.

Correlations between serum GH and IGF-I, IGFBP-1, and IGFBP-3 levels. Before the start of DEXA, no correlation was found between gestational age, birth weight, birth weight SD score, and serum levels of IGF-I, IGFBP-1, and IGFBP-3. Mean, baseline, and maximal serum GH levels also did not correlate with serum IGF-I, IGFBP-1, and IGFBP-3 levels. No correlation was found between serum levels of IGF-I and IGFBP-1 or IGFBP-3 levels.

During DEXA treatment, however, serum IGFBP-1 levels were significantly correlated with mean and baseline GH levels ($r = 0.71$, $p = 0.03$ and $r = 0.70$, $p = 0.04$, respectively), but not with serum IGF-I levels. Ventilation score and nutritional intake did not significantly correlate with serum GH, IGF-I, IGFBP-1, and IGFBP-3 levels, neither before nor after the start of DEXA treatment.

DISCUSSION

In this study we demonstrate a significant decline in serum baseline, mean, and maximal GH levels and serum IGFBP-1 levels in ventilated very preterm infants 2 d after the start of DEXA treatment. Two days of DEXA treatment had no significant acute effect on serum IGF-I and IGFBP-3 levels. So far, no studies have described the effect of 2 d of high-dose DEXA administration on GH secretion, serum IGF-I levels, and serum IGFBPs in ventilated very preterm infants.

It has been reported that DEXA treatment in preterm infants results in reductions in weight gain, growth in occipitofrontal head circumference, linear growth, and lower leg growth; has a catabolic effect by increased protein breakdown; and alters skeletal metabolism (3–8, 20–22). Despite substantial concerns questioning the benefits of the use of postnatal steroids and concerns about long-term neurologic outcome raised by

Table 1. *Clinical data before and during DEXA treatment in 10 very preterm infants with BPD*

	Pretreatment		During DEXA	
	Median	Range	Median	Range
Weight (g)	1092	750–2265	1125	695–2195
Postconceptional age (wk)	29.6	27.6–34.6	30.5	2.1
Postnatal age (wk)	2.1	1.0–3.6	2.4	1.4–4.0
Doses of DEXA (*n*)	–		5	3–7
Cumulative DEXA dosage (mg/kg)	–		1.23	0.76–1.7
Ventilation score	454*	240–1700	210	105–1024
Energy intake (kcal/kg per day)	97.3	64.2–144.3	118.7	43.6–144
Protein intake (kcal/kg per day)	2.6	1.9–3.9	2.7	1.9–3.9
Fat intake (g/kg per day)	4.9	1.4–8.6	5.2	0.6–9.6

* $p < 0.05$.

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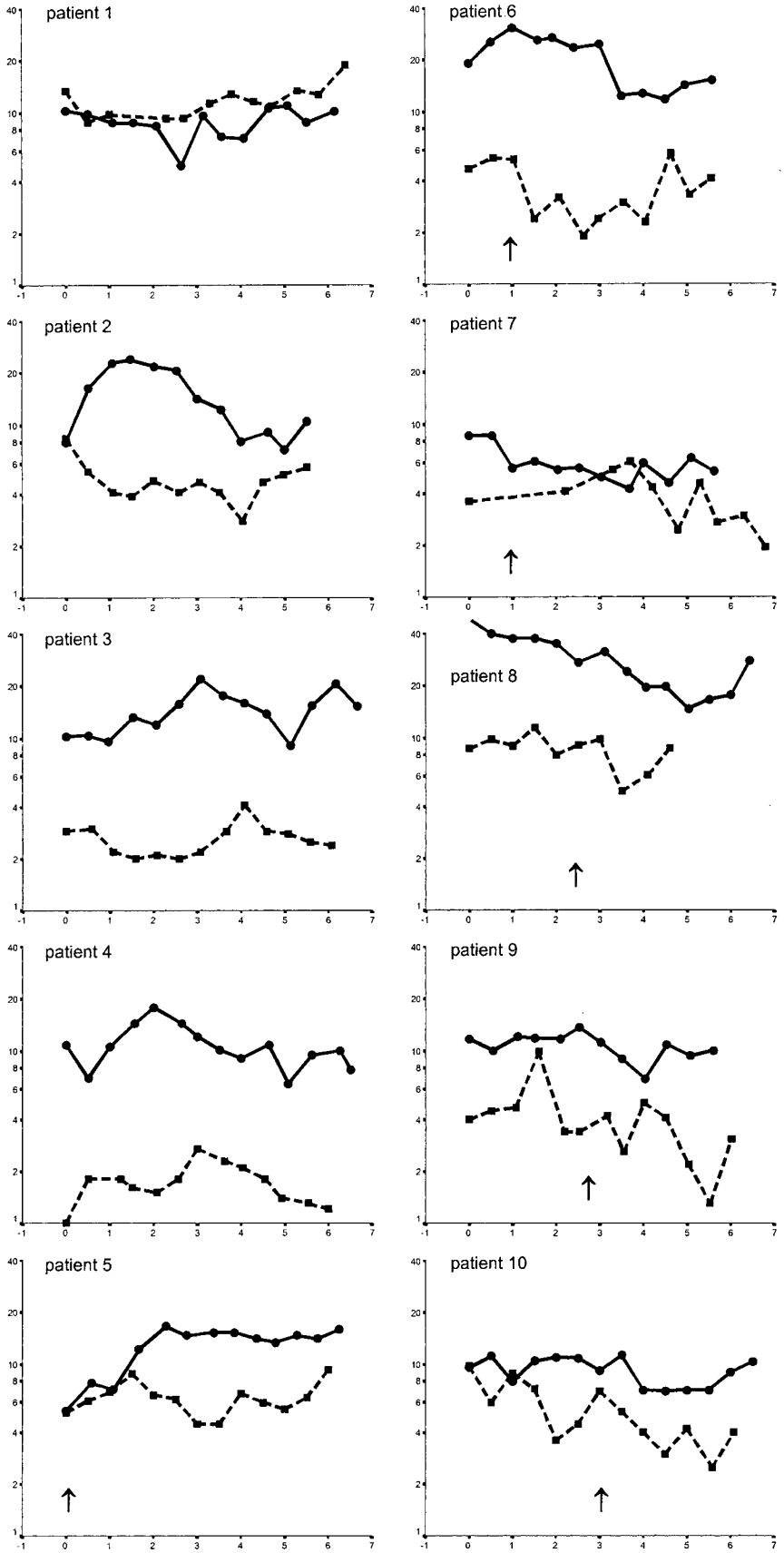

Figure 1. GH profiles in ventilated preterm infants before (●—●) and during (■---■) DEXA treatment. GH levels are expressed in micrograms per liter on a logarithmic scale against time in hours. In patients 1–5, time $t = 0$ corresponds to 6, 5, 2.5, 0.5, and 0 h after DEXA administration, respectively. In patients 6–10, ↑ corresponds with time of DEXA administration.

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Table 2. *Characteristics of GH profile, IGF-I, and binding proteins before and during DEXA in 10 very preterm infants with BPD*

	Pretreatment		During Treatment	
	Median	Range	Median	Range
GH profile				
Baseline GH (μg/L)	11.3	5.7–28.6	3.8*	1.7–11.8
Mean GH (μg/L)	12.0	6.0–28.4	4.4*	1.7–11.9
Max GH (μg/L)	17.3	8.7–48.9	8.9†	2.7–18.8
IGF-I (ng/mL)	32.9	22.2–89.5	36.3	19.9–65.8
IGFBP-1 (ng/mL)	69.6	23.2–341.4	13.5*	8.2–62.6
IGFBP-3 (mg/L)	0.6	0.4–1.2	0.6	0.4–1.0

Serum GH levels calculated by Pulsar analysis.
* $p < 0.01$ compared with levels before DEXA.
† $p < 0.05$ compared with levels before DEXA.

the American Academy of Pediatrics and Canadian Paediatric Society (23), DEXA is still administered to preterm infants to wean them from the ventilator when clinical and radiologic signs of BPD develop and conservative treatment, such as increased ventilation settings, fluid restriction, diuretics, antibiotics, and inhalation therapy, has failed. The starting dose of DEXA usually given to very preterm infants in most neonatal intensive care units is 0.5 mg/kg per day for 3 d, which is equivalent to 13.3 mg/kg per day of hydrocortisone or 3.3 mg/kg per day of prednisone. Thus, compared with other corticosteroid treatments, the DEXA dose used in preterm infants is 11- to 22-fold higher than in children with kidney transplants (prednisone, 0.15–0.25 mg/kg per day) or in physiologic replacement in relative adrenal insufficiency in very preterm infants (1.2 mg of hydrocortisone in a 1000-g infant). Besides, the biologic half-time of DEXA is much longer than that of prednisone (36–72 h compared with 8–12 h) (24).

Inasmuch as we present the first data of an acute DEXA effect on serum GH levels in preterm infants, we cannot compare our results with other studies in preterm infants. In older individuals the effects of glucocorticoids on spontaneous and stimulated GH secretion appear contradictory (25–27). Chronic hypercortisolism inhibits spontaneous and stimulated GH secretion in children and adults (9–11, 28). Hokken-Koelega *et al.* (29) demonstrated a significant decrease in mean GH levels during chronic prednisone administration in pediatric growth-retarded renal allograft recipients. In contrast, acute administration of DEXA increases spontaneous GH secretion in children and adults (30–33). In rats, spontaneous GH levels were significantly decreased and the GH-releasing hormone–induced GH response was blunted after 4 d of DEXA treatment. Subsequent immunologic neutralization of somatostatin, however, resulted in a significantly enhanced GH response, suggesting that steroids inhibit the GH response to GH-releasing hormone by increasing the hypothalamic somatostatin secretion (27). Miell *et al.* (34), however, found in healthy volunteers a persistent but attenuating rise in serum GH levels after 4 d of DEXA treatment. This different effect of DEXA administration compared with our data might be caused by the 10-fold lower dosage of DEXA (0.05 mg/kg per day) used by Miell *et al.* (34) than the dosage used in our preterm infants. Thus, the potentiating or blocking effect of DEXA on GH secretion seems to be dependent on the duration and dose of administration of DEXA.

We could not demonstrate a relationship between the serum GH levels and the cumulative dose or the number of doses of DEXA given before the second profile. This might be because of the small variation in the cumulative dose in our patients. The suppressive effect of DEXA on serum GH levels in most infants was still present 12 h after the last dose, suggesting a GH-suppressive effect of at least 12 h in most infants. In children undergoing renal transplantations, the suppressive effect of prednisone on GH secretion was similar whether given as daily or alternate day prednisone therapy, suggesting a prolonged effect of prednisone administration. As the biologic half-life of DEXA is much longer and the dose of DEXA given to our patients much higher compared with the prednisone dose in the renal allograft patients, we speculate that the suppressive effect on serum GH levels might be at least 24 h.

After 2 d of high-dose DEXA treatment, we could not demonstrate a decline in serum immunoreactive IGF-I and IGFBP-3 levels whereas serum GH levels significantly de-

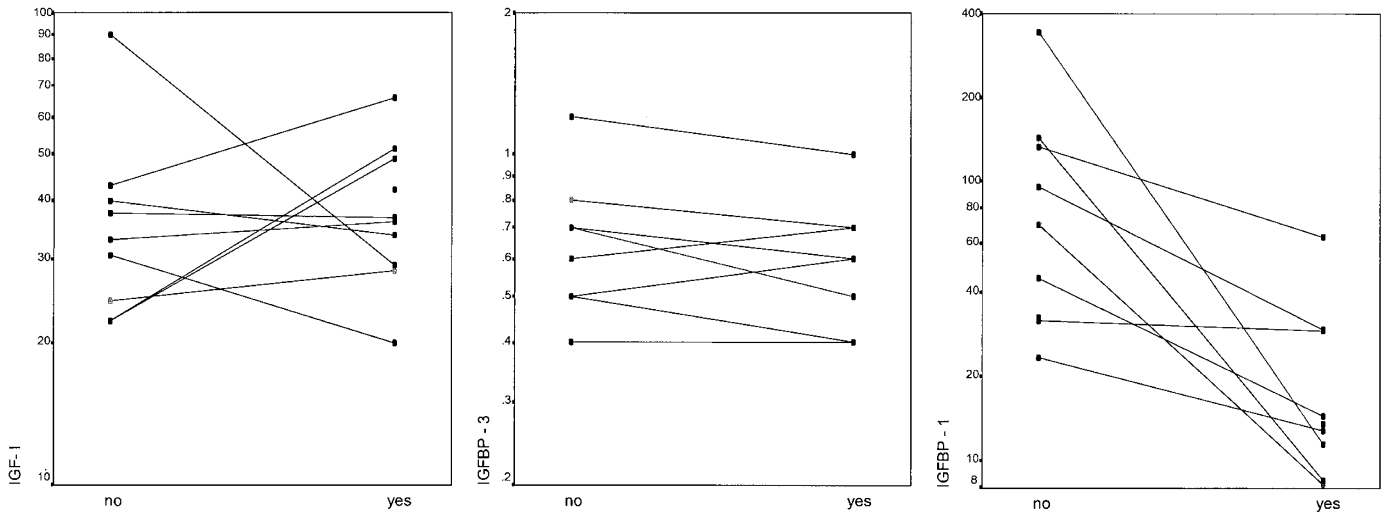

Figure 2. Effect of DEXA treatment on serum IGF-I, IGFBP-3, and IGFBP-1 levels in ventilated preterm infants. Serum IGF-I is expressed in nanograms per milliliter, serum IGFBP-3, in milligrams per milliliter, and serum IGFBP-1, in nanograms per milliliter.

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clined. We had expected to find the decline in serum GH levels being accompanied by a decline in serum IGF-I levels. However, it might be that 2 d of DEXA treatment was too short to observe an acute decline in serum IGF- I or IGFBP-3 levels. It was not possible to perform the second GH profile at a later moment during DEXA treatment as most infants did not retain their arterial catheter once they were extubated. Pretreatment IGF-I levels were low already, with high serum GH levels, suggesting a relatively GH-resistant state; this might also explain the apparent lack of effect of DEXA on circulating IGF-I. Serum IGF-I levels might also be more influenced by nutritional intake (35). Data on the effect of DEXA on serum IGF-I and IGFBP-3 levels in preterm infants are limited. Serum IGF-I and IGFBP-3 levels have been reported to rise in preterm infants after cessation of DEXA treatment (5, 20). Bloomfield *et al.* (22) showed increasingly higher levels of IGF-I and IGFBP-3 with reducing dosages of DEXA, suggesting a dose-dependent effect of DEXA on IGF-I and IGFBP-3 levels. However, in these studies, at all time points during and after DEXA treatment, serum IGF-I and IGFBP-3 levels were higher than before the start of DEXA and therefore not lower than baseline values. Our study showed that there was no decline in serum IGF-I and IGFBP-3 levels at least after 2 d of DEXA treatment. Because none of the studies had an untreated control group, no data are available about the IGF-I and IGFBP-3 levels from patients with similar respiratory problems when no DEXA has been started. The higher levels of IGF-I and IGFBP-3 observed after stopping DEXA might not be merely caused by cessation of steroids but also by other factors such as improvement in the clinical condition and nutritional intake of the infants (35).

In this study we did not observe a relationship between serum IGF-I and IGFBP-3, in contrast to other studies in older children. Whether this is related to the developmental range of the infants or other factors needs further study.

The high pretreatment IGFBP-1 levels observed in our patients might be related to their severe illness as has been described in older children (36). High IGFBP-1 levels are also found in conditions such as prolonged fasting, anorexia nervosa (37), and fetal hypoxemia (38). The high IGFBP-1 levels in our study were not caused by fasting as all our preterm infants were continuously fed and never showed low glucose levels. We cannot rule out a possible additional effect of short-term hypoxemia on serum IGFBP-1 levels immediately before starting DEXA treatment. The observed decline in serum IGFBP-1 levels during DEXA treatment in our patients agrees with Miell *et al.* (39), who described an increase in serum insulin levels accompanied by a decrease in serum IGFBP-1 after short-term DEXA treatment in adults. As it has been demonstrated that insulin and not glucose levels are regulating serum IGFBP-1 levels *in vivo* (40, 41), we speculate that high insulin levels during DEXA might have resulted in a decline in serum IGFBP-1 as observed in our patients. However, as some of our patients were extubated after 2 d of DEXA, thereby showing clinical improvement, this might also have contributed to the decrease in serum IGFBP-1 levels.

The GH-IGF axis in childhood is important for growth, but the precise role of GH and IGF-I in preterm infants is as yet unknown. DEXA treatment is known to reduce physical growth and to induce catabolism. Although our study showed a significant decline in serum GH levels after 2 d of DEXA, no acute decline in serum immunoreactive IGF-I levels was seen. This is in agreement with other studies (5, 20, 22). It therefore remains a question whether the low GH levels observed after the start of DEXA are responsible for the decline in growth rate in these preterm infants. It might well be that the decline in growth is rather the result of a direct effect of DEXA on the epiphyseal cartilage by inhibition of the local secretion and paracrine action of IGF-I (12). Prednisone causes *in vitro* a 46% fall in IGF bioactivity and has a suppressive effect on IGF mRNA in the tibia, liver, lung, and kidney in the rat, without causing significant changes in serum IGF-I levels (42, 43). Thus, DEXA-induced inhibition of local IGF-I gene expression might be one of the mechanisms of growth retardation as well. In addition the low serum GH levels might result in a diminished direct effect on the epiphyseal plate as well (12).

CONCLUSIONS

In conclusion, our data show a suppressive effect of 2 d of DEXA treatment on serum GH levels, without an acute decline in serum IGF-I levels. A concomitant decline in serum IGFBP-1 levels was found.

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