Effect of dexamethasone on the IGFBP-1 regulation in premature infants during the first weeks of life

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Background: Early glucosteroid treatment in preterm infants has a negative impact on physical growth and development. So far, data on dexamethasone effect on the GH/IGF axis and the clinical outcome are conflicting.

Objective: Therefore, we studied the effect of dexamethasone treatment on parameters of somatic growth and on the secretion of insulin like growth factors (IGFs) and insulin like growth factors binding proteins (IGFBPs) in preterm infants.

Methods: In 75 preterm infants somatic development was assessed at birth and after 3 months of corrected age. IGF-I/II and IGFBP-1-3 were measured at the same time. According to their treatment regime the infants were assigned to the dexamethasone treated or the non-treated group.

Results: At 3 months the 13 infants with dexamethasone had a lower body weight, slightly lower body length and a lower head circumference. IGF-II (464.4 ± 97.4 vs 638 ± 201.4 µg/l, p = 0.001) and IGFBP-3 (1800 ± 426 vs 2105 ± 547 µg/l, p = 0.045) were significantly reduced under the influence of glucocorticoids, whereas IGFBP-1 was elevated (59.6 ± 61.0 vs 21.1 ± 21.7 µg/l, p = 0.002). The ratio IGFBP-3/(IGFBP-1 + 2) was reduced in the dexamethasone group (1.827 ± 0.868 vs 3.098 ± 1.898 µg/l, p = 0.016), implying a significant retardation in the somatic development.

Conclusion: Dexamethasone impairs IGF and IGFBP secretion and stimulates IGFBP-1, an inhibitor of IGF-I. These pathways might contribute to alterations of the GH/IGF axis, particularly the ratio IGFBP-3/(IGFBP-1 + 2).

Keywords: dexamethasone, IGF, IGFBP-1, preterm infants, growth

Introduction

Dexamethasone is a potent glucocorticoid commonly used in the prevention and treatment of chronic lung disease of prematurity. However severe side effects are of clinical concerns (Bloomfield et al 2001).

In 1998, Yeh et al reported a significant increase of neurological dysfunction in preterm infants treated with dexamethasone, in boys growth was reduced, additionally (Yeh et al 1998). In consequence, glucocorticoid-therapy in neonatal patients was critically re-evaluated: Between 1994 and 2001 the use of dexamethasone dropped from 22% to 6%. Chronic lung disease increased from 13% to 17%, whereas neonatal mortality declined from 21% to 15% (Shinwell et al 2003).

Postnatal therapy with glucocorticoids result in favorable and non-favorable consequences: Ventilation time and the rate of bronchopulmonal dysplasia are reduced (Tsukahara et al 1999; Sweet and Halliday 2000), whereas the risk for impaired neurological development, cerebral paresis, metabolic disorders, hypertrophic cardiomyopathy, reduced growth and perforations of the gastrointestinal tract is increased

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(Romagoli et al 1999; Sweet and Halliday 2000; Stark et al 2001). Dexamethasone treatment within the first 24 hours did not influence survival or lung disease in preterm infants between 500 g and 1000 g (Stark et al 2001).

According to Halliday, the negative impact of dexamethasone becomes particularly evident when applied within the first 96 hours of life (Halliday 2004). In contrast, the moderate use of glucocorticoids beginning at 7–14 days after birth might result in a beneficial outcome at the age of 15 years in former preterm infants with a birth weight <1250 g (Gross et al 2005).

The potential growth restricting effects of dexamethasone may be mediated via suppression of the IGF axis. Both dexamethasone dose and treatment regimen influence circulating IGF-1 and IGFBP-3 levels (Bloomfield et al 2001).

Postnatal dexamethasone therapy influences IGFBPs concentrations: within the first 8 weeks of life IGFBP-3 and phosphoisoforms of IGFBP-1 were reduced, the latter only in children with elevated insulin levels (Kajantie et al 2002). Growth hormone and IGFBP-1 concentrations were decreased in preterm children with bronchopulmonal dysplasia two days after the beginning of dexamethasone treatment compared to pre-dexamethasone levels (Huysman et al 2003).

IGFBP-1 mRNA secretion was induced by glucocorticoids in different animal models by various pathways (Luo et al 1990; Suwanichkul et al 1994; Suh et al 1995; Suh and Rechler 1997; Uchijima et al 1999; Lewitt 2001; Gan et al 2005).

Objective

Early glucocorticoid treatment might alter infants growth via the IGF/IGFBP axis. We therefore studied the influence of dexamethasone on the clinical outcome and on the secretion of IGFs and IGFBPs in preterm infants after of 3 months.

Methods

Patients

75 preterm infants of our neonatal intensive care were included in this investigation. Blood was drawn at the second day of life and at the corrected age of 3 months. The following data were collected and analysed: gestational age, auxologic parameters (body weight, length, and head circumferences), mode of cardiopulmonary adjustment (APGAR scores, pH of umbilical vessels, oxygen saturation), therapeutic strategies (respiratory support).

The patients were assigned to the dexamethasone-treatment group or non-treatment group depending, if they received treatment with glucosteroids or not. Dexamethasone treatment (n = 13) was initiated because of bronchopulmonary dysplasia (n = 8) or long-term ventilation with expected difficulties during the weaning from mechanical ventilation (n = 5), respectively.

Glucocorticoid treatment was performed as a 3-day tapering course of dexamethasone with a total dose of 1.35 mg/kg according to Garland et al given between the 2nd and 4th week after birth (Garland et al 1999).

After discharge from the hospital, the formerly risk-infants underwent controls to monitor development and identify developmental deviations during a short hospital stay (2–3 days) at the corrected postnatal age of three months.

Infants with congenital malformations, inherited metabolic disorders, and infants of diabetic mothers were excluded.

Measurements of IGF and IGFBPs

Venous blood samples (residual volumes from routine checks) were investigated.

Samples for the first cross-section analysis ("after birth") were taken on the second day after birth. All venous blood samples were taken at 07.00 am, the infants received their last enteral feeding between 04.30 and 05.00 am. IGFs and IGFBPs were evaluated using commercially available radioimmunoassays (IGF-I, IGFBP-1, IGFBP-3: Fa. Mediagnost, Tübingen, Germany; IGF-II, IGFBP-2: Fa. DSL, Sinsheim, Germany).

The ratio IGFBP-3/(IGFBP-1 + 2) was estimated as a marker for the shift from fetal to adult IGF pattern described earlier (Hübler et al 2006).

Basal growth hormone (GH) levels were not determined because of the strong fluctuation of basal GH values.

Statistical analysis

Statistical analysis was conducted using the SPSS release 12.0 statistics package (SPSS Inc., USA). Values are shown as percentage or mean + standard deviation (SD), as indicated. The Mann-Whitney U-test was used for statistical determinations, with $p < 0.05$ considered as significant.

The study was approved by the ethics committee of the Friedrich-Schiller-University of Jena (No. 0381-11/99).

Results

At birth, the infants treated with dexamethasone had a smaller head circumference, lower APGAR scores, a longer

ventilation time and needed O_2 supplementation for a longer time ($p < 0.05$, Mann-Whitney test).

After 3 months body weight and head circumference were still significantly reduced in the dexamethasone group ($p < 0.05$, Mann-Whitney U test) (Table 1).

Dexamethasone treatment was related to reduced IGF-II and IGFBP3 secretion and to an increased IGFBP-1. No significant differences were found for IGF-I and IGFBP-2 ($p < 0.05$, Mann-Whitney U test) (Table 2).

IGFBP-1 secretion was significantly enhanced by dexamethasone treatment, both in the infants with or without bronchopulmonary dysplasia (BPD). In contrast, BPD did not influence the IGFBP-1 levels neither in the treated nor in the non-treated group ($p < 0.05$, Mann-Whitney U test) (Figure 1).

The ratio IGFBP-3/(IGFBP-1 + 2) was significantly reduced in the infants with glucocorticoid administration ($p < 0.05$, Mann-Whitney U test) (Figure 2).

Discussion

Dexamethasone has a negative impact on the somatic development in preterm infants. At the age of 3 months steroid treated neonates had a significantly reduced body weight and head circumference and tend to be smaller.

Table 1 Birth characteristics and anthropometric measurements at three months of corrected age

Parameter	Systemic glucocorticoid treatment		Mann-Whitney U (p-value)
	no (n = 62)	yes (n = 13)	
At birth			
Gestational age (weeks)	33.3 ± 2.0	31.2 ± 3.9	0.050
Body weight (g)	1831 ± 467	1521 ± 631	0.081
Body length (cm)	42.9 ± 3.9	40.4 ± 5.3	0.085
Head circumference (cm)	30.4 ± 2.6	28.1 ± 3.5	0.033*
APGAR after 1 minute	6.5 ± 1.8	4.7 ± 2.5	0.013*
APGAR after 5 minutes	8.1 ± 1.3	6.8 ± 1.8	0.010*
Ventilation (hours)	46.3 ± 165.4	300.6 ± 449.4	0.001*
O_2-supplementation (days)	5.2 ± 20.4	24.6 ± 36.4	0.001*
pH of the umbilical artery	7.28 ± 0.06	7.23 ± 0.11	0.138
At 3 months			
Body weight (g)	5672 ± 990	4874 ± 1175	0.024*
Body length (cm)	59.9 ± 4.3	58.0 ± 6.1	0.354
Head circumference (cm)	40.2 ± 2.1	39.1 ± 2.0	0.037*
Daily weight gain (g/day)	28.1 ± 4.9	24.9 ± 5.7	0.100
Daily length gain (cm/day)	0.12 ± 0.02	0.12 ± 0.02	0.677
Daily head growth (cm/day)	0.072 ± 0.015	0.073 ± 0.015	0.098

Table 2 Insulin-like growth factors and IGF binding proteins at three months of corrected age

Parameter	Systemic glucocorticoid treatment		Mann-Whitney U (p-value)
	no (n = 62)	yes (n = 13)	
IGF-I [μg/l]	73.3 ± 27.7	69.1 ± 34.4	0.520
IGF-II [μg/l]	638.4 ± 201.6	464.4 ± 97.4	0.001*
IGFBP-1 [μg/l]	21.1 ± 21.7	59.6 ± 61.0	0.002*
IGFBP-2 [μg/l]	842.2 ± 392.8	1119.0 ± 840.1	0.212
IGFBP-3 [μg/l]	2105 ± 547	1800 ± 426	0.045*

After stopping dexamethasone daily weight gain, occipital-frontal circumference and crown-rump length improved significantly in ventilated babies with BPD in a Canadian investigation. The weekly dose of dexamethasone was correlated negatively with all physical growth measures (Skinner et al 1997).

In piglets dexamethasone significantly reduced absolute gain in weight and length. At least in parts, this effect could be reversed by growth hormone, which indicates a serious negative impact of glucosteroids on the growth hormone/IGF axis (Ward et al 1998). Dexamethasone treatment for chronic lung disease restricts linear growth, which might be mediated via systemic effects on the IGF-I axis. Glucocorticoid treatment in general and specifically the dexamethasone dose reduce serum IGF-I and IGFBP-3 significantly (Bloomfield et al 2001).

In the dexamethasone treated children the secretion of IGF-II and IGFBP-3 was significantly reduced after 3 months of life, whereas IGF-I levels were only slightly, but not significantly reduced. Kajantie et al could demonstrate similar findings for IGFBP-3 during the first 2 months (Kajantie et al 2002). Off steroid treatment, mean serum IGF-I and IGFBP-3 increased in a cohort of 10 ventilated infants with BPD, the weekly dose of dexamethasone showed no correlation with growth factors in this investigation (Skinner et al 1997).

In human fibroblast dexamethasone blocks IGFBP-3, IGFBP-4 and IGFBP-5 mRNA transcription (Connover et al 1995), in hepatocytes IGF-I mRNA (El-Khattabi et al 2003). So, glucosteroids interfere with the GH/IGF transcription axis on the cytoplasmatic level.

In the infants treated with dexamethasone IGFBP-1 levels were significantly enhanced, irrespectively if they were diagnosed BPD or not.

Kajantie et al (2002) reported reduced IGBP-1 phosphoisoforms in children with elevated insulin

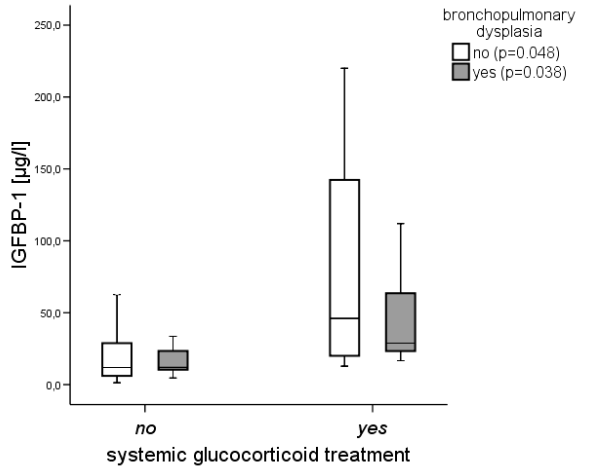

Figure 1 IGFBP-1 [µg/l] after 3 months of corrected postnatal age in the subgroups of infants without bronchopulmonary dysplasia (n = 60; no glucocorticoids n = 55; glucocorticoids n = 5), and with bronchopulmonary dysplasia (n = 15; no glucocorticoids n = 7; glucocorticoids n = 8). Results of the Mann-Whitney U-test are given for each subgroup.

secretion. However, neither the age of the children during glucocorticoid therapy nor the impact of the child's age on the IGFBP-1 concentration within the first 2 months of life was addressed in their investigation. But, both factors might be of relevant influence. Dexamethasone seems to induce IGFBP-1 secretion with a latency of some weeks after application. Five days after dexamethasone and colostrum application IGF-I increased and IGFBP-1 and IGFPBP-2 decreased in neonatal calves. According to Sauter et al this might be the expression of a maturation of the somatotropic axis (Sauter et al 2003). IGFBP-1 was reduced 1 and 2 weeks after dexamethasone and GH therapy, but 7 weeks after treatment IGFBP-1 concentrations were significantly elevated (Hammon et al 2003).

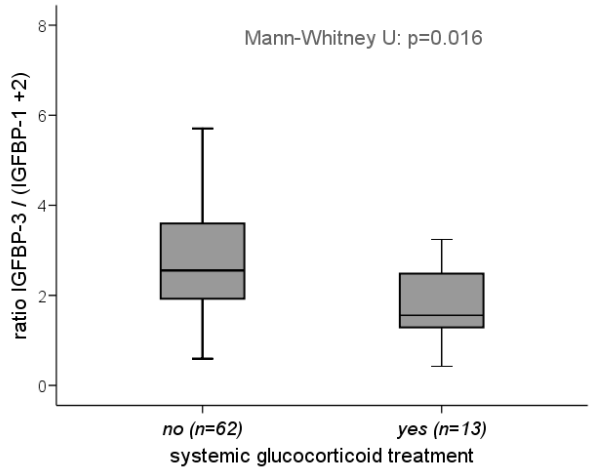

Figure 2 Box-Whisker plots of the IGFBP-3/(IGFBP-1 + 2) ratio in the subgroups of infants with or without a systemic administration of glucocorticoids given between the 2nd and 4th week after birth.

In contrast to our data, Huysman et al found a reduction of IGFBP-1 only 2 days after the beginning of dexamethasone application in preterm infants with BPD on ventilation (Huysman et al 2003). It remains to speculate that Huysman's data reflect only a very short term effect of the steroids on the IGFBP-1 secretion, whereas our findings integrate a longer and more sustainable effect. IGFBP-1 is known to have a negative effect on the function of IGF-I. IGFBP-1 is lower in infants AGA (appropriate for gestational age) than in IUGR (intrauterine growth retardation) with catch up growth and even lower compared to those IUGR without catch up growth (Öszkan et al 1999).

In several animal models cascades of IGFBP-1 mRNA could be induced by stimulation of IGFBP-1 promoter activity (Suwanichkul et al 1994; Gan et al 2005), via the insulin-independent kinases (Lewitt 2001), by stabilisation of IGFP-1 mRNA (Luo et al 1990; Uchijima et al 1999) and a synergy of the glucocorticoid receptor and the hepatocyte nuclear factor 1 (HNF1) (Suh and Rechler 1997; Suh et al 1995). These pathways would let us expect an increase of IGBP-1 in the steroid treated children. As IGFBP-1 is thought to decrease the effect of IGF-I (Öszkan et al 1999), this pathway might contribute to reduced physical growth in dexamethasone treated infants.

Earlier, we have shown that the first months of life are characterized by a pole reversal of the somatotropic axis: IGFBP-1 and 2 decrease and IGFBP-3 increases. The ratio IGFBP-3/(IGFBP-1 + 2) is therefore a marker for the maturation of the IGF/IGFBP axis. In infants with BPD this ratio is significantly reduced during the first 6 months of life (Hübler et al 2006).

As glucocorticoid treatment is linked to a significantly reduced ratio, both in infants with and without BPD, dexamethasone contributes to the delay of somatic maturation in high risk infants.

We suggest different phases of the interaction between dexamethasone and the IGF/IGFBP-1 axis:

Phase 1: The metabolic decompensation after glucocorticoid application causes hyperglycemia, reactive hyperinsulinism and eventually reduction of serum IGFBP-1.

Phase 2: Dexamethasone induces the hepatic synthesis of IGFBP-1.

Phase 3: After a latency serum IGFBP-1 increases. This might lead to an impaired equilibrium between the IGF-binding-proteins and therefore might contribute to endocrine dysregulation due to a reduced number of freely circulating IGFs.

These alterations might possibly persist (potential phase 4) and alter somatic growth and eventually contribute to metabolic syndrome and cardiovascular disease.

In our investigation, dexamethasone treatment has a negative impact on weight gain and head circumference. Our data might contribute to understand the pathophysiological mechanisms involved in these development, particularly the IGF/IGFBP axis.

It remains to speculate if low weight at the age of 3 months might be associated with excessive weight gain later on and therefore with an increased risk for metabolic and cardiovascular disease (Barker et al 2005).

Conclusion

Dexamethasone treatment might contribute to impaired somatic maturation in high risk infants via alterations in the IGF/IGBP axis. Therefore, the use of glucocorticoids in neonatology should be carefully weighed. Long-term follow-up of our infants should evaluate further somatic development and cardiovascular function.

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