The placenta as modulator of fetal prosperity
Buimer, M.

Citation for published version (APA):
Chapter 4:

Postnatal administration of dexamethasone for weaning off the ventilator affects thyroid function

M. Buimer, A.G. van Wassenaer, J.H. Kok

*Neonatology, in press © 2008 S.Karger AG, Basel*
Abstract

Background: Very preterm neonates are at risk of hypothyroxinemia because of prematurity as well as because of neonatal disease. Hypothyroxinemia is associated with impaired developmental outcome. Preterm infants who cannot be weaned from the ventilator can be treated with dexamethasone. Glucocorticoid administration has been found to alter thyroid hormone parameters. Therefore, dexamethasone treatment in these infants might additionally impair their thyroid function, which could have consequences for developmental outcome.

Objective: To assess what changes in thyroid function occur in the first hours after initiating dexamethasone treatment in ventilated preterm infants.

Methods: Preterm infants, in whom the decision was taken to start dexamethasone treatment, were included. Thyroxin, T₃, rT₃, TSH and Cortisol were determined before and 6 to 9 after administration of the first dose of a postnatal dexamethasone course. Details of clinical condition were recorded at both time points.

Results: Sixteen very preterm infants were included at a median age of 20 days. While clinical condition was stable between start of dexamethasone and 6-9 hours thereafter, TSH and T₃ levels decreased significantly. ReverseT₃ levels significantly increased, resulting in a decrease of the T₃/rT₃ Ratio. There was no statistically significant effect on the levels of T₄.

Conclusion: Postnatal dexamethasone administration negatively affects thyroid function in the preterm infant with severe chronic lung disease.
Postnatal Dexamethasone Affects Thyroid Function

Introduction

Dexamethasone treatment in ventilated preterm infants has been demonstrated to rapidly reduce requirements for oxygen and ventilation, decreasing the incidence of chronic lung disease. In contrast, dexamethasone treatment has also been identified as an independent risk factor for delayed psychomotor development. These data from follow-up studies are in agreement with observations from animal experiments, in which abnormal neuronal growth as well as increased white matter damage is observed after dexamethasone treatment.

Normal brain development is dependent on sufficient and continuous provision of thyroid hormone. Preterm neonates are at risk of hypothyroxinemia, especially in case of respiratory and infectious diseases. Follow-up of preterm neonates shows a higher prevalence of developmental disabilities, when postnatal thyroid hormone levels have been lower, and this is reason for an ongoing debate on the necessity of thyroid hormone supplementation. Dexamethasone is found to alter thyroid function in adult human as well as in animal experiments. These effects comprise a direct Hypothalamic-Pituitary-Thyroid axis effect, but also thyroid hormone metabolism is influenced, evidenced by altered Deiodinase activity in cultured brain cells as well as in the chicken embryo. Interestingly, dexamethasone can both increase and decrease Deiodinase type III (D3), depending on species, tissue localization and developmental stage. Therefore dexamethasone might either result in more as in less bio-active hormone (T3). In a recent paper antenatal glucocorticoids were associated with higher T4 concentrations in the first week after birth, while Williams et al found that postnatal dexamethasone administration was associated with significantly lower fT4 and T3 concentrations in the third week of life. The aim of the present study was to assess direct effects of dexamethasone treatment on thyroid function in ventilated, very preterm infants.

Patients and Methods

This prospective exploratory study, performed between September 1st, 2000 and June 1st, 2004, included preterm neonates admitted to the NICU ward of the Academic Medical Center who could not be weaned from the ventilator and had an indication for a course of dexamethasone according to the attending neonatologist. Our preliminary estimates of eligible infants, based on department records, were of about 20 dexamethasone-treated infants per year, our intended study size. However, as is also the experience in other studies investigating postnatal glucocorticoids, the inclusion rate dropped about 4-fold because of increasing clinical concerns about the harmful effects on brain development of dexamethasone treatment. This caused our inclusion phase to take almost 4 years, while the decision to treat infants with dexamethasone was increasingly restricted to those with the most severe respiratory complications. A three weeks tapering course of
dexamethasone was prescribed with a starting dose of 0.25 mg/kg/day, the total dexamethasone dose of a full course being 4 mg/kg. This decision was generally taken when despite optimal treatment of fluid balance and possible infectious comorbidity, there was no change in ventilatory settings and the chest X ray showed signs of chronic lung disease. After informed consent of the parents, preterm infants were enrolled. The study protocol was approved by the institutional review board of the Academic Medical Center.

Blood Samples
A baseline blood sample, within 2 hours before administration of the first dose of dexamethasone, and a second sample 6 to 9 hours after the first dose of dexamethasone was taken. One ml of peripheral blood was collected, either from capillary puncture or from an arterial line. Blood was centrifuged immediately and stored at -20°C until assay. In some cases the amount of blood was limited and hormone analysis was incomplete. In each sample $T_3$, rT3, $T_4$, TSH and Cortisol were determined; in case of a limited amount of plasma priority was given in the order mentioned.

Clinical Data
Clinical data on ventilation, circulatory support, patent ductus arteriosus, cerebral damage and medication, at baseline and at the time of the second blood sample, as well as obstetric and neonatal data at birth were collected. Follow up data included assessment of neurodevelopmental outcome until 3 years of age, using the Bayley Scales of Infant Development II and neurological examination.

Assays
$T_3$, $T_4$, and rT3 were measured by in-house RIA methods. Detection limits were 5.0, 0.3 and 0.03 nmol/l, respectively; intra-assay coefficients of variation were 2-4%, 3-4% and 4-5%, respectively, and interassay coefficients of variation were 3-6%, 7-8% and 5-9%, respectively. TSH was measured by time-resolved fluoroimmunoassay (Delfia hTSH Ultra, Wallac Oy, Turku, Finland). Detection limit was 0.01 mU/l, intra-assay coefficient of variation was 1-2% and inter-assay coefficient of variation was 3-4%. Cortisol was measured by ELISA (Immulite analyzer, DPC, Los Angeles, CA, U.S.A.). Detection limit was 50 nmol/l, intra-assay and inter-assay coefficient of variation at 200 nmol/L were 6.4% and 9 %, respectively, and 5.8% and 7%, respectively, at 370 nmol/l.

Statistical Analysis
Data were analyzed using the statistical program SPSS 11.5.1 for Windows (SPSS Inc., Chicago, Ill). Hormone values before and after administration of dexamethasone were compared using Wilcoxon signed ranks test as these values turned out not to be normally distributed, as indicated by one sample Kolmogorov-Smirnov test. Due to availability of plasma, two Cortisol values (“< 50 nmol/l”), one $T_3$ value (“< 0.6 nmol/l”) as well as two
Postnatal Dexamethasone Affects Thyroid Function

TSH determinations (one was “< 0.04 mU/l” and, due to lack of material for a dilution step the other was classified as “< 0.1 mU/l”) could only be determined by approximation, mentioning threshold values. Therefore, the Wilcoxon signed ranks tests were performed once with the target value equaling this threshold value, and a repeated, substituting the target value by 50% of this threshold value. As the substitution did not affect the rank, both approaches gave an identical result. Clinical parameters before and after initiation of treatment were compared using Wilcoxon signed ranks test, whereas clinical parameters of subgroups according to the T₃ / rT₃ Ratio were compared using Mann Whitney U test. Linear regression analysis and Pearson correlation were used in correlations of continuous variables. P-values < 0.05 were considered statistically significant.

Results

In the study period, 24 infants were eligible for the study. Four infants could not be included because dexamethasone administration had started before consent could be obtained. Two parent couples declined consent. Finally, eighteen infants were enrolled in the study. In one baby, blood was erroneously taken 90 minutes after dexamethasone administration, results were excluded. In another infant, the small amount of blood of a second sample taken 9 hours after dexamethasone administration, results were also omitted from the Tables and the analysis.

Table 1 shows the obstetric and neonatal data at admission of the 16 babies analyzed. All infants were born at or less than 29 weeks gestational age. The age at which dexamethasone was started differed considerably (9-48 days after birth with 81% of the infants at 13-27 days after birth). In most infants dexamethasone administration started in the afternoon, while the second sample was generally taken in the evening.

Table 2 shows the median hormone values and range before and after the first dose of dexamethasone. TSH decreased statistically significantly after dexamethasone administration. We observed no statistically significant change of T₄. There was a significant decrease of T₃ and a significant increase of rT₃, after initiation of dexamethasone, resulting in a statistically significant decrease in the T₃ / rT₃ Ratio. Postmenstrual age had a significant positive correlation (Pearson r = 0.57, p=0.02) with the T₃ / rT₃ Ratio before treatment, in concordance with literature. Figure 1 depicts the changes of the T₃ / rT₃ Ratio before and after Dexamethasone treatment as a function of postmenstrual age. Eleven out of fifteen T₃ / rT₃ Ratios decreased, in four infants the T₃ / rT₃ Ratio increased. Review of clinical neonatal variables in these four infants showed significantly lower T₃ levels (mean 0.4 vs. 1.0 nmol/L, p=0.002) and lower systolic blood pressures at baseline (mean 35 vs. 52 mmHg, p=0.02).
Chapter 4

Clinical Characteristics at birth

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N = 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA at birth (weeks)</td>
<td>27½/7 (24½/- - 29)</td>
</tr>
<tr>
<td>Mode of delivery Vaginal / Caesarean</td>
<td>7/9</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>828 (615 – 1470)</td>
</tr>
<tr>
<td>Antenatal Corticosteroids</td>
<td>15</td>
</tr>
<tr>
<td>Apgar 5</td>
<td>8 (2-10)</td>
</tr>
<tr>
<td>Intubated &lt; 1 hour after birth</td>
<td>12</td>
</tr>
<tr>
<td>Surfactant treatment</td>
<td>11</td>
</tr>
</tbody>
</table>

Characteristics upon inclusion

<table>
<thead>
<tr>
<th>Characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first dose (days)</td>
<td>20 (9 - 48)</td>
</tr>
<tr>
<td>PMA (weeks)</td>
<td>29½/- (27½/- - 34½/-)</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>905 (710 -1630)</td>
</tr>
<tr>
<td>Weight increase since birth (g)</td>
<td>113 (-135 – 380)</td>
</tr>
<tr>
<td>Duration of ventilation (days)</td>
<td>17 (4 – 33)</td>
</tr>
<tr>
<td>Ventilation: HFO / Conventional</td>
<td>13 / 3</td>
</tr>
<tr>
<td>Patent Ductus Arteriosus</td>
<td>6 †</td>
</tr>
<tr>
<td>Receiving Dopamine</td>
<td>3</td>
</tr>
<tr>
<td>Receiving Dobutamine</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral abnormalities on ultrasound</td>
<td>8 #</td>
</tr>
</tbody>
</table>

Table 1: Clinical Characteristics at birth, and upon inclusion
Values are median (range) or N, as appropriate. † Including one infant that underwent operative closure of ductus 3 days before dexamethasone course. # One infant with Periventricular Leukomalacia (grade 1) four infants with Intraventricular Hemorrhage grade 3 and three infants with Subependymal Hemorrhage (IVH grade 1).

Cortisol levels statistically significantly decreased by almost 50%, as expected.29 In order to be certain that the thyroid hormone changes found were not caused by changes of the clinical condition,30 we compared circulatory and ventilatory parameters of the infants before and at the time of collection of the second blood sample. Blood pressure values rose after start of dexamethasone therapy (median systolic pressure 49 and 52, and median diastolic pressure 27 and 35 mmHg before and after treatment, respectively, p= 0.003). Ventilatory parameters before initiation of dexamethasone and at the time of collection of the second blood sample did not change. The dosage of dopamine, which was administered to 3 infants, as well as dobutamine (administered to one infant) remained unaltered at the time of collection of the second sample, compared to dosage before initiation of dexamethasone. Table 3 shows individual clinical data as well as follow up data until 3 years of age. Only in one infant no follow up data were available. Of the remaining 15 children outcome was good in only three. Three infants died during or shortly after dexamethasone treatment, two infants had disabling Cerebral Palsy (CP), 5 infants had mild neurological abnormalities or non-disabling CP in combination with mental and/or motor delay and another two infants showed some motor or mental delay or behaviour problems with normal neurological examination.
Postnatal Dexamethasone Affects Thyroid Function

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>before</th>
<th>N</th>
<th>after</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>16</td>
<td>2.55 (&lt;0.1 – 6.8)</td>
<td>15</td>
<td>1.2 (&lt;0.04 – 3.3)</td>
<td>0.017</td>
</tr>
<tr>
<td>T₄</td>
<td>15</td>
<td>70 (35-120)</td>
<td>15</td>
<td>70 (30 - 95)</td>
<td>NS</td>
</tr>
<tr>
<td>T₃</td>
<td>16</td>
<td>0.85 (0.3 – 1.55)</td>
<td>15</td>
<td>0.75 (0.4 – 1.5)</td>
<td>0.022</td>
</tr>
<tr>
<td>rT₃</td>
<td>16</td>
<td>0.78 (0.5 – 1.7)</td>
<td>16</td>
<td>0.95 (0.5 – 1.85)</td>
<td>0.025</td>
</tr>
<tr>
<td>T₃ / rT₃</td>
<td>16</td>
<td>1.14 (0.29–2.1)</td>
<td>15</td>
<td>0.80 (0.45 – 1.4)</td>
<td>0.012</td>
</tr>
<tr>
<td>Cortisol</td>
<td>14</td>
<td>150 (&lt;50 - 720)</td>
<td>12</td>
<td>80 (50 - 510)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Table 2: Hormone levels before and after Dexamethasone. Values are median (range). T₄, T₃, rT₃, and Cortisol in nmol/l; TSH in mU/l. † Wilcoxon signed ranks test.

Figure 1: Changes in the T₃ / rT₃ Ratio before and after Dexamethasone treatment.

T3 / rT3 Ratio

Increase or decrease of T₃ / rT₃ Ratio at baseline and after the first dose of Dexamethasone in relation to postmenstrual age.
Table 3: Individual Characteristics at birth, during hospital admission at and after inclusion.

<table>
<thead>
<tr>
<th>Infant</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
<th>f</th>
<th>g</th>
<th>h</th>
<th>i</th>
<th>j</th>
<th>k</th>
<th>l</th>
<th>m</th>
<th>n</th>
<th>o</th>
<th>p</th>
</tr>
</thead>
</table>

**Birth characteristics**

- **Gestational age at birth (weeks):**
  - a: 27 5/7
  - b: 27 3/7
  - c: 25
  - d: 27 6/7
  - e: 26 1/7
  - f: 27 6/7
  - g: 25
  - h: 27 1/7
  - i: 26 3/7
  - j: 27 4/7
  - k: 26 1/7
  - l: 24 5/7
  - m: 28 2/7
  - n: 27 2/7
  - o: 27 7/7

- **Birth weight (g):**
  - a: 615
  - b: 645
  - c: 1350
  - d: 1145
  - e: 740
  - f: 945
  - g: 810
  - h: 715
  - i: 820
  - j: 1150
  - k: 880
  - l: 615
  - m: 835
  - n: 980
  - o: 1470

- **BWR:**
  - a: 0.94
  - b: 0.93
  - c: 0.68
  - d: 1.02
  - e: 0.93
  - f: 0.63
  - g: 1.04
  - h: 1.02
  - i: 0.91
  - j: 1.05
  - k: 0.52
  - l: 0.63
  - m: 1.30

**Clinical data before starting dexamethasone treatment**

- **Time on ventilator (days):**
  - a: 13
  - b: 15
  - c: 19
  - d: 18
  - e: 26
  - f: 4
  - g: 14
  - h: 13
  - i: 10
  - j: 14
  - k: 33
  - l: 20
  - m: 26
  - n: 27
  - o: 23

- **Surfactant treatment:**
  - Y = yes; N = no
  - a: Y
  - b: Y
  - c: Y
  - d: Y
  - e: Y
  - f: Y
  - g: Y
  - h: Y
  - i: Y
  - j: Y
  - k: Y
  - l: Y
  - m: Y

- **Cerebral abnormalities on ultrasound:**
  - IVH = Intraventricular haemorrhage
  - SEH = Subependymal haemorrhage
  - - = No abnormality
  - a: IVH
  - b: SEH
  - c: SEH
  - d: -
  - e: -
  - f: -
  - g: -
  - h: -
  - i: IVH
  - j: FL
  - k: -
  - l: IVH
  - m: SEH

**Data at start dexamethasone treatment**

- **Age (days):**
  - a: 15
  - b: 22
  - c: 19
  - d: 19
  - e: 27
  - f: 9
  - g: 22
  - h: 13
  - i: 19
  - j: 8
  - k: 19
  - l: 9
  - m: 48
  - n: 21
  - o: 27
  - p: 27
  - q: 24

- **Body weight (g):**
  - a: 715
  - b: 710
  - c: 1350
  - d: 1290
  - e: 845
  - f: 810
  - g: 1190
  - h: 800
  - i: 820
  - j: 1150
  - k: 1000
  - l: 740
  - m: 965
  - n: 1145
  - o: 1630
  - p: 830

- **Receiving Dopamine:**
  - Y = yes; N = no
  - a: Y
  - b: N
  - c: Y
  - d: Y
  - e: Y
  - f: Y
  - g: Y
  - h: Y
  - i: N
  - j: N
  - k: N
  - l: N
  - m: N
  - n: N
  - o: N

- **TSH (mU/L):**
  - a: < 0.1
  - b: 0.36
  - c: 0.36
  - d: 2.1
  - e: 2.7
  - f: 0.76
  - g: 2.7
  - h: 0.39
  - i: 4.4
  - j: 4.4
  - k: 4.8
  - l: 4.5
  - m: 6.8
  - n: 2.85
  - o: 4.9
  - p: 0.32
  - q: 2.7

- **T3 (nmol/L):**
  - a: 0.35
  - b: 1.05
  - c: 1.05
  - d: 1.95
  - e: 1.2
  - f: 0.8
  - g: 0.9
  - h: 0.3
  - i: 0.3
  - j: 0.65
  - k: 1.1
  - l: 1.15
  - m: 0.65
  - n: 1.3
  - o: 0.75
  - p: 1.1

- **rT3 (nmol/L):**
  - a: 1.2
  - b: 1.7
  - c: 1.05
  - d: 0.87
  - e: 0.87
  - f: 0.8
  - g: 0.7
  - h: 1.4
  - i: 0.65
  - j: 0.5
  - k: 0.75
  - l: 0.8
  - m: 0.55
  - n: 0.95
  - o: 1.15
  - p: 0.65

**Clinical course during dexamethasone treatment**

- **Time to extubation (days):**
  - a: NA
  - b: 7
  - c: 4
  - d: 9
  - e: 3
  - f: 1
  - g: 8
  - h: 2
  - i: 4
  - j: 8
  - k: 1
  - l: 18
  - m: 3
  - n: 3
  - o: 25
  - p: 1

- **Died during or shortly after dexamethasone treatment:**
  - a: +
  - b: +
  - c: +
  - d: +
  - e: +
  - f: +
  - g: +
  - h: +
  - i: +
  - j: +
  - k: +
  - l: +
  - m: +

**Abnormal neurodevelopmental outcome at age 3 years**

- **NA: not applicable.**

Cerebral abnormalities on ultrasound: FL = Flaring; SHE = Subependymal haemorrhage; IVH = Intraventricular haemorrhage; PVL = Periventricular leukomalacia.

Surfactant treatment, Receiving Dopamine, Died during or shortly after dexamethasone treatment: Y = yes; N = no PDA requiring treatment: Patent ductus arteriosus requiring treatment, M = Medical treatment; S = Surgical treatment. Abnormal neurodevelopmental outcome at age 3 years: Abnormal outcome was defined as +++ severely abnormal if infant had disabling (non-ambulant) CP, ++ abnormal if there were mild neurological abnormalities or non-disabling CP in combination with mental and/or motor delay >3 months, + mildly abnormal if neurological examination was normal but if there was motor or mental delay or behaviour problems, N normal if none of the above occurred.

The four infants the T3 / rT3 Ratio increased instead of decreasing were infant a, h, i, and m.
Discussion

In this study we were able to demonstrate clinically relevant and statistically significant changes of dexamethasone on thyroid function. Two regulatory thyroid mechanisms play a role. The first was on the pituitary level, indicated by lower TSH levels. This suppressive effect is in accordance with literature reports on effects of glucocorticoids.\(^{31,32}\) The second effect was on the level of peripheral thyroid hormone metabolism reflected in changes in T\(_3\) and rT\(_3\). Normally after birth a gradual decrease of rT\(_3\) and an increase of plasma T\(_3\) is seen in the first week of life, compatible with a decrease in D3 activity.\(^{28}\) The changes we found (decrease of T\(_3\), increase of rT\(_3\)) were opposite, implicating inactivation of thyroid hormone. It is unlikely that these changes are a consequence of decreased production of thyroid hormone, as T\(_4\) levels did not differ. Most probably this effect was caused by stimulation of D3. Alternatively this can be explained by inhibition of Deiodinase type 1, but this is less likely as levels of T\(_4\) remained unchanged. It is well known that D3 tissue levels in premature infants are still high,\(^{33}\) even more so in ill premature infants.\(^{34}\)

Also in the chicken embryo animal model, dexamethasone was shown to stimulate D3.\(^{20,21}\) This contrasts to findings under experimental conditions where dexamethasone leads to suppression of D3.\(^{35}\) Whether dexamethasone leads to induction or suppression of D3 apparently depends, apart from species and tissue, on ontogenetic phase.\(^{22,23,33}\) Although all of the found changes could also have been caused by deterioration of the clinical condition, we could not find such a change in the time window between start of dexamethasone and 6 to 9 hours thereafter. On the contrary, we recorded a stable respiratory course accompanied by a somewhat higher blood pressure. The four infants in which the low T\(_3\) / rT\(_3\) Ratio raised after dexamethasone treatment had comparatively low T\(_3\) levels, possibly indicating an already increased activity of D3 at baseline.\(^{34}\) Our study is the first to demonstrate direct thyroid hormone-related side effects of dexamethasone. The study design, in which each infant served as its own control permitted to find the above described effects.

In a next step, it must be examined whether the identified acute changes are persistent, and how they change during the dexamethasone course, and beyond. Since development of the preterm brain is dependent on continuous provision of thyroid hormone concerns seem justified, as another study demonstrated dexamethasone to decrease T\(_3\)\(^{27}\), but also FT\(_4\) concentrations in premature infants at day 14 of life.\(^{25}\) In the animal model it has been shown that D3 is abundantly present in brain astrocytes,\(^{36}\) therefore local thyroid hormone delivery in brain tissue could be impaired during dexamethasone administration. In that case the side effect we found could be one of the mechanisms by which dexamethasone can impair psychomotor development. Indeed neurodevelopmental outcome of our study group was not normal in most infants.
Our study design is not appropriate to make any statement on the causal factors. Dexamethasone is likely to play a role, however in combination with the severe illness all these infants experienced. Current practice in prescribing dexamethasone has changed, not only has the dose been decreased, dexamethasone is to a greater extent prescribed as a last rescue medicine.

In summary, we have demonstrated possible harmful effects of dexamethasone on thyroid hormone regulation and metabolism in preterm infants with severe respiratory disease. If these effects persist throughout the complete dexamethasone course, they aggravate the already present transient hypothyroxinemia of prematurity.
Reference List


3. O'Shea TM, Kothadia JM, Klinepeter KL, Goldstein DJ, Jackson BG, Weaver RG, III et al. Randomized placebo-controlled trial of a 42-day tapering course of dexamethasone to reduce the duration of ventilator dependency in very low birth weight infants: outcome of study participants at 1-year adjusted age. Pediatrics 1999;104:15-21.


27. Wiersinga, W. M. The peripheral conversion of thyroxine (T4) into triiodothyronine (T3) and reverse triiodothyronine (rT3). Thesis, University of Amsterdam 1979.
Postnatal Dexamethasone Affects Thyroid Function
