CLINICAL STUDY

Changes in plasma thyroid hormone levels after a single dose of triiodothyronine in premature infants of less than 30 weeks gestational age

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Abstract

Objective: Evaluation of thyroid hormone response to a single administration of triiodothyronine (T₃) early postnatally to premature infants of <30 weeks gestational age.

Design: A prospective clinical trial with historical control.

Methods: Ten infants born <28 weeks gestational age and ten infants born between 28 and 30 weeks gestational age were given 0.5 µg/kg T₃ intravenously at 12 h after birth. The infants <28 weeks gestational age were also treated with thyroxine (T₄; 8 µg/kg, once daily) during the first 6 weeks of life. Premature infants from a previous trial served as a matched historical control group. Analysis of variance for repeated measurements was performed.

Results: For the infants 28–30 weeks gestational age mean plasma T₃ concentrations were significantly higher in the T₃-treated group ($P = 0.027$) for at least 2 weeks, whereas mean plasma levels of T₄, free T₄ and TSH were comparable. For the infants <28 weeks gestational age plasma T₃ levels were also significantly different after correction for gestational age ($P = 0.0002$), with either comparable or higher values in the T₃-treated infants up to 56 days after injection of T₃. Mean plasma free T₄ levels were lower during the first 3 days and higher or comparable thereafter ($P = 0.0014$), and TSH suppression was more evident in the T₃-treated infants ($P = 0.003$).

Conclusion: A single administration of T₃ to premature infants <30 weeks gestational age early postnatally results in a sustained increase of plasma T₃ levels during the first weeks of life. In infants of 28–30 weeks gestational age this occurs without change in plasma free T₄ levels, whereas in infants <28 weeks gestational age a transient decrease of plasma free T₄ was present. The increase in plasma T₃ is possibly caused by a T₃-induced increase of type I deiodinase activity.

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Introduction

Transient hypothyroxinemia is a common finding in the first weeks of life in premature infants (1–3). It is characterised by low levels of thyroxine (T₄) and triiodothyronine (T₃), in the presence of normal levels of thyrotropin (TSH). The degree of hypothyroxinemia depends on the gestational age (GA) and the severity of disease, resulting in lower T₄ levels in the younger and the more severely ill infants (2). It is believed to be caused, at least in part, by immaturity of the hypothalamic–pituitary–thyroid axis and by the abrupt discontinuation of transplacentally transferred maternal T₄ (4). The significance of the hypothyroxinemia remains unclear, and whether it is appropriate to treat or not to treat, is still a subject of debate (5). However, both low T₄ and low T₃ levels in premature infants have been associated with poor neurological

and developmental outcome in several studies (6–12). A recent randomized controlled trial of T₄ supplementation in premature infants in our institution and one from a Belgian group failed to show any improvement in neurodevelopmental outcome (13, 14). However, in our trial T₄ supplementation seemed to be associated with an improvement in mental developmental outcome in the subgroup of infants of less than 27 weeks gestation (13). Besides increasing plasma T₄ and free T₄ levels, T₄ supplementation resulted in a suppression of TSH levels, whereas plasma T₃ levels did not increase (15), but, on the contrary, decreased (16). It is believed that the low plasma T₃ level in premature infants is related to low activity of the type I deiodinase (DI), which is responsible for the endogenous production of T₃ by an outer ring deiodination of T₄ to T₃ (17). Another explanation for the low T₃ levels, however, could be a higher elimination rate of T₃ by the type III

deiodinase (DIII), which is abundantly present in fetal tissues (18–20) and is responsible for the deiodination of T_3 to diiodothyronine. As a result, T_3 concentrations remain low in preterm infants early in life. Moreover, sulfation of iodothyronines remains active in very preterm infants, as during the fetal period (21, 22). These sulfoconjugates are metabolized by DI and as a consequence of the low DI activity high circulating levels can be found in fetal/preterm life. It has been suggested that sulfated T_3 could serve as a local source of T_3 in fetal tissues containing sulfatase.

There is evidence that DI is responsive to T_3 itself. Higher T_3 concentrations enhance deiodinase activity (23). Thus, administration of T_3 could result in a sustained increase of plasma T_3 as a result of higher DI levels and thereby increased endogenous conversion of T_4 to T_3 .

Because in our former trial T_4 supplementation was not beneficial in infants between 28 and 30 weeks GA, but seemed to improve neurodevelopmental outcome in infants <28 weeks GA (24), two groups were present in this study. The aim of the study was to investigate whether a single administration of T_3 given to premature infants <30 weeks GA shortly after birth, could result in a sustained increase of plasma T_3 concentrations. Infants 28–30 weeks GA were given only T_3 . Infants <28 weeks GA were given T_3 , and subsequently received T_4 during the first weeks of life according our former protocol (13).

Our results indicate that a single T_3 dose shortly after birth indeed results in a sustained increase in plasma levels of T_3 .

Subjects and methods

Study population

Infants admitted to the Neonatal Intensive Care Unit of the Academic Medical Centre in Amsterdam (The Netherlands) who were born between April and October 1998 with a GA <30 weeks were eligible for the study. Infants were excluded if they had a severe congenital anomaly. Ten infants born <28 weeks GA, and ten infants born at 28 weeks or later, but before the 30th week of gestation were recruited. If informed consent had been obtained from at least one of the parents within 12 h of birth, the infant was included in the study.

This study was approved by the Committee of Medical Ethics of the Academic Medical Centre in Amsterdam.

Intervention

Infants 28–30 weeks GA The infants born between 28 and 30 weeks GA received a single dose of T_3 (Liothyronine, 2.5 $\mu\text{g}/\text{ml}$; manufactured by the hospital pharmacy) of 0.5 $\mu\text{g}/\text{kg}$ birthweight, administered

as a bolus intravenously at 12 h after birth (range 10–14 h). They were not treated with T_4 , unless the plasma free T_4 level dropped below 10 pmol/l, our lower limit of the reference group (unpublished), during the first 3 weeks of life. If T_4 treatment appeared to be necessary, it was to be continued until the postnatal age of 42 days.

Infants <28 GA The study infants born before the 28th week of gestation received a single intravenous dose of T_3 (0.5 $\mu\text{g}/\text{kg}$ birthweight) at 12 h after birth (range 10–14 h). In addition, they received T_4 (Levothyroxine, 25 $\mu\text{g}/\text{ml}$; manufactured by the hospital pharmacy) at a dose of 8 $\mu\text{g}/\text{kg}$ birthweight once daily during the first 6 weeks of life, starting 24 h after birth. T_4 was given intravenously until the infant was on full enteral feeding, and orally thereafter.

Assays

Whenever available, cord blood was obtained. A 0.5 ml blood sample was drawn 2 and 6 h after the administration of T_3 for the measurement of T_3 . Blood samples (1 ml) were taken at 24 h and again on day 3, day 7, day 14 and day 21. When the infant was on T_4 treatment, a blood sample was also obtained at day 42 and day 56. In all specimens T_4 , free T_4 , T_3 , reverse T_3 , TSH and thyroxine binding globulin (TBG) were determined. The assays used have been described previously (15).

Blood pressure was measured either with an indwelling arterial catheter or using a non-invasive oscillometric pressure monitor (Dinamap, Critikon, The Netherlands). Blood pressure and heart rate were noted at hourly intervals and values were retrieved retrospectively from the patient's charts.

Historical control group

As controls, study patients from the previous trial with T_4 were used (13). In this trial, which occurred at the same Neonatal Intensive Care Unit between January 1991 and July 1993, 200 infants of <30 weeks GA were randomized to treatment with T_4 (8 $\mu\text{g}/\text{kg}$ once daily during the first 6 weeks of life) or placebo. For the infants in the present study born <28 weeks GA, infants from the treatment group of the T_4 trial were taken as controls, whereas for the infants between 28 and 30 weeks GA, infants from the placebo group were taken as controls. Control infants were matched for gestational age group and for antenatal treatment with corticosteroids.

Statistics

Data of heart rate and blood pressure were analysed using the paired *t*-test. Differences in the time course of hormone levels between treatment and control group

were tested using analysis of variance for repeated measurements (BMDP 5V), in which hormone levels were analysed as a function of time, T₃ administration, gestational age and an interaction term between T₃ administration and time. A significant interaction term was also considered as an effect of treatment. Statistical significance was set at a P value of 0.05.

Results

The clinical characteristics of the study patients and the historical control group prior to and following the intervention are shown in Table 1. For the group of infants ≥ 28 weeks GA, mean GA was slightly higher (29.4 versus 28.9 weeks, $P = 0.02$), and they received parenteral nutrition for a little longer. For the group of infants < 28 weeks GA, the mean gestational age was lower in the treatment group compared with the control group (26.3 versus 27.0 weeks, $P = 0.01$). They were also intubated more frequently at birth ($P = 0.03$), were ventilated for a longer period of time (17.7 versus 6.6 days, $P = 0.16$) and received more parenteral nutrition (23.7 versus 17.0 days, $P = 0.03$). Although these differences could be explained by the lower mean GA alone, changes in treatment policies in our unit could also be partially responsible.

Infants 28–30 weeks GA

In Fig. 1 the time course of mean plasma concentrations of T₃, T₄, free T₄ and TSH for the infants born between 28 and 30 weeks GA is shown. The plasma concentration of T₃, measured 2 h after the administration, was 2.33 nmol/l, decreasing to 1.83 nmol/l

and then further to 1.57 nmol/l at 6 and 12 h after T₃ administration respectively. Plasma T₃ levels were constantly and significantly higher in the T₃-treated infants compared with control infants ($P = 0.027$). Plasma T₄ and free T₄ levels were not significantly different. It is clear that a single dose of T₃ to infants between 28 and 30 weeks GA does not lead to TSH suppression. Thus, a single T₃ administration resulted in higher plasma T₃ levels, without changing the concentrations of T₄, free T₄ and TSH. Also, reverse T₃ and TBG levels were comparable between the two groups (data not shown). As none of the infants ≥ 28 weeks GA needed treatment with T₄, data beyond 21 days of life were not available in this gestational age group.

Infants < 28 weeks GA

Figure 2 shows the time course of the mean plasma concentrations of T₃, T₄, free T₄ and TSH for the infants < 28 weeks GA. The mean plasma levels of T₃ was 2.65 nmol/l 2 h after the administration, decreasing to 1.61 nmol/l and 1.31 nmol/l at 6 and 12 h after injection respectively. As the mean GA in the T₃ group is lower than in the control group, constantly lower plasma T₃ levels in the T₃-treated infants were to be expected. However, plasma T₃ levels were either comparable or higher in this group. Indeed, the two curves were significantly different after correction for gestational age ($P = 0.0002$ for the effect of T₃ and $P = 0.0001$, interaction term). At day 56 the difference between the T₃ treated group and the control group was 1.0 nmol/l (2.8 versus 1.8 nmol/l). The time course of T₄ was significantly different between

Table 1 The clinical characteristics of the study patients and the historical control group prior to and following the intervention.

	<28 weeks GA			28–30 weeks GA		
	Treatment (T ₄ ⁺ T ₃ ⁺) (n = 10)	Control (T ₄ ⁺ T ₃ ⁻) (n = 28)	P	Treatment (T ₄ ⁻ T ₃ ⁺) (n = 10)	Control (T ₄ ⁻ T ₃ ⁻) (n = 37)	P
Birthweight (g)*	926 (32)	973 (37)	0.5	1243 (61)	1249 (35)	0.9
Gestational age (weeks)*	26.3 (0.2)	27.0 (0.1)	0.01	29.4 (0.1)	28.9 (0.1)	0.02
Male/female [†]	7/3	15/13	0.4	6/4	21/16	0.8
Apgar score after 5 minutes*	6.2 (0.7)	8.5 (1.6)	0.03	8.4 (0.5)	8.9 (1.2)	0.6
Intubation at birth (n) [‡]	8 (80)	11 (39)	0.03	1 (10)	6 (16)	0.3
Surfactant therapy (n) [‡]	4 (40)	8 (29)	0.8	2 (20)	9 (24)	0.6
Time on mechanical ventilation [#] (days)*	17.7 (6.8)	6.6 (6.2)	0.2	3.4 (2.0)	2.2 (3.2)	0.6
Time on parenteral nutrition [#] (days)*	23.7 (4.0)	14.9 (8.5)	0.03	17.4 (2.5)	13.1 (6.5)	0.07
Oxygen dependency at 28 days postnatal age (n) [‡]	6 (60)	17 (61)	0.4	3 (30)	7 (19)	0.5
Oxygen dependency at 36 weeks postconceptional age (n) [‡]	2 (20)	5 (18)	0.7	0 (0)	3 (8)	0.3
Intraventricular hemorrhage grade 3 and 4 (n) [‡]	1 (10)	6 (21)	0.7	0 (0)	2 (5)	0.9
Cystic periventricular leucomalacia (n) [‡]	2 (20)	0 (0)	0.1	0 (0)	0 (0)	
Septicaemia (n) [‡]	6 (60)	6 (21)	0.06	4 (40)	8 (22)	0.2
Death (n) [‡]	3 (30)	4 (14)	0.4	0 (0)	3 (8)	0.4

Values are expressed as *mean $\pm$ S.E.M., [‡]percentage of total study population or [†]number of patients.

[#] Data analysed only of surviving infants.

the two groups ($P = 0.021$, interaction term) with somewhat lower T_4 levels in the T_3 group. Plasma levels of free T_4 were lower during the first 3 days and higher or comparable thereafter in the T_3 group. The free T_4 time course was again significantly different between both groups ($P = 0.0014$, interaction term). The TSH suppression was more evident in the T_3 group ($P = 0.003$, interaction term), but both groups showed an adequate TSH increase of approximately 2.5-fold in response to withdrawal of T_4 supplementation. There were no differences in plasma reverse T_3 levels and TBG levels between T_3 -treated and control infants (data not shown).

While maximum T_3 levels were measured 14–16 h after birth, no clinically significant changes in heart

rate and blood pressure were seen in either gestational age group during the first 72 h of life.

Discussion

We hypothesized that in premature infants born <30 weeks GA, who commonly have a transient hypothyroxinemia, a single administration of a relatively high dose of T_3 early postnatally, could result in an appropriate provision of T_3 to all tissues that need T_3 in the transition from intrauterine to extrauterine life. By intravenous injection of T_3 , the increase in plasma level will depend on the T_3 distribution volume and the half life of plasma T_3 . On administering $0.5 \mu\text{g/kg}$ T_3

Figure 1 Plasma concentrations of T₃ (a), T₄ (b), free T₄ (c) and TSH (d) in infants born between 28 and 30 weeks gestational age. Values presented are means $\pm$ S.E.M. ■ treatment group (T₄⁻ T₃⁺), □ control group (T₄⁻ T₃⁻). For the treatment group, mean plasma concentrations of T₄ and T₃ in cord blood are based on six samples, and mean plasma concentrations of free T₄ and TSH in cord blood are based on seven samples. The arrow indicates the administration of a single dose of T₃ at a postnatal age of 12 h.

(or 770 pmol/kg, molecular weight being 650), about 2.5–3.0 pmol/ml plasma was present after 2 h, indicating a large distribution volume. This is in accordance with the distribution volume for T₃ described in adults (25). Moreover, the rapid decline of T₃ after injection indicates a short half life time of plasma T₃. In this respect it is remarkable that in T₃-treated infants plasma T₃ levels remain significantly higher during the first weeks of life compared with control infants, giving the impression of an increased T₃ production compared with control infants.

Thus, our results suggest that a single T₃ administration to premature infants <30 weeks GA causes a sustained increase in plasma T₃ levels during the first weeks of life. For infants between 28 and 30 weeks GA, this increase of T₃ occurred without any effect on plasma T₄ and free T₄ levels. For infants <28 weeks

GA, however, both T₄ and free T₄ decreased transiently, and TSH was somewhat more suppressed. This could be the result of the T₃ injection or the small differences in gestational age and severity of disease between the treatment and control group.

In term newborn infants a T₃ rise normally occurs during the first day of life, which is believed to be caused mainly by enhanced thyroidal excretion as a result of the early postnatal TSH surge (21). There is evidence that T₃ itself induces DI activity, as was found in experiments in mice (23) and men (26), and in FTRL-5 cell cultures (27). We postulated that the thyroidal T₃ surge thus causes an increase in liver and/or thyroidal DI resulting in an increased rate of T₃ production. Preterm infants have a much lower T₃ surge (21) and also an immature deiodinating system with low DI (21) and/or high DIII activity (28). Indeed,

their plasma T_3 is much lower than in full term infants during the first 4–6 weeks of life (2). The single T_3 administration shortly after birth imitates the postnatal T_3 surge. Although levels of T_3 are still below the levels in term infants, T_3 is increased compared with historical controls. This can be explained by the induction of conversion of T_4 to T_3 through enhanced DI activity by T_3 itself. The fact that the effect on plasma T_3 occurs both in a situation of TSH suppression, as in the infants <28 weeks GA under T_4 supplementation, and in a situation of normal TSH levels, as in the infants 28–30 weeks GA, may suggest that extrathyroidal, rather than thyroidal DI is activated by T_3 injection.

There is only little experience with T_3 treatment in premature infants. In a case control study Eggermont

et al. treated 10 premature infants with a mean GA of 28.7 weeks with 5 $\mu\text{g/kg/d}$ of T_3 during 6 weeks (29). Schönberger *et al.* (30) studied the effect of the combined treatment with T_4 (25 μg) and T_3 (5 μg) in 45 premature infants in a quasi-randomized manner. Both studies used much higher doses of T_3 , and administered T_3 on a daily basis during a period of time. Although the methodology of these studies was far from optimal, positive clinical results from the treatment were claimed (30).

We are aware that, because of the trial design, comparability between the infants of the present study, who were born in 1998, and the historical control group, who were recruited between 1991 and 1993, is not optimal. More recent data from our unit about the spontaneous course of thyroid hormones in premature

Figure 2 Plasma concentrations of T₃ (a), T₄ (b), free T₄ (c) and TSH (d) in infants born at <28 weeks gestational age. Values presented are means $\pm$ S.E.M. ■ treatment group (T₄⁺ T₃⁺), □ control group (T₄⁺ T₃⁻). All values of mean plasma concentrations in cord blood in the treatment group are based on only two samples. The arrow indicates the administration of a single dose of T₃ at a postnatal age of 12 h. T₄ was administered from day 1 until day 42.

infants were not available. We have shown (2) that, of both thyroid hormones, T₄ decreases most in infants of lower GA or higher morbidity. Plasma T₃ follows the changes of T₄ to a lesser extent. On the basis of the plasma T₄ levels, which were either similar in both groups (infants 28–30 weeks GA) or lower in the T₃-treated group as compared with the control group (infants <28 weeks GA), we conclude that the higher T₃ levels found in the study infants were probably related to the T₃ injection, and not to differences in patient characteristics or treatment policies. The results

need to be confirmed in a randomised set up. Possible positive effects on clinical outcome can then be studied.

The present study was designed to investigate the effects of T₃ administration on thyroid hormone levels. Any clinical effect of treatment with T₃ should be evaluated with a randomized controlled clinical trial. We did not see any significant clinical side effects during the study period. Blood pressure and heart rate did not change with the increased plasma T₃ levels. In our former T₄ trial we found that heart rate was increased in the T₄ group, especially in infants <28 weeks GA. The

combined results of our two studies point towards local T_4 to T_3 conversion in cardiomyocytes by type II deiodinase (DII). Indeed, the presence of DII in human cardiac muscle has been described (31).

Conclusion

Our results indicate that a single administration of T_3 to premature infants of less than 30 weeks GA, given shortly after birth, results in a sustained increase of plasma T_3 levels during the first weeks of life. In infants 28–30 weeks GA this occurs without any effect on plasma T_4 and free T_4 . In infants of <28 weeks GA, a transient decrease of T_4 and free T_4 is present, which could be due to the T_3 administration or to clinical factors. The single T_3 injection is not associated with clinically important negative side effects.

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