Efficacy of a high initial dose of L-thyroxine in the treatment of congenital hypothyroidism

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Abstract

Results of a treatment strategy using an initial dosage of 10 – 15 µg/kg/day of L-thyroxine was evaluated in a prospective longitudinal study in King Khalid University Hospital, Riyadh, Saudi Arabia. Thyroid-stimulating hormone (TSH) and free-thyroxine (FT4) measurements being taken at 3 weeks, 6 weeks, 3 months, 6 months, 9 months and one year of the start of therapy. Forty-two newborns with confirmed primary congenital hypothyroidism (CH), detected by neonatal screening, were treated with the same therapeutic strategy (10 – 15 µg per kg per day). Twenty-one (50%) ectopic, 13 (31%) athyreotic, and 8 (19%) eutopic with in-creased uptake. A mean L-thyroxine dosage of 11.3 µg per kg per day (range 9.7 – 14.7) at the onset of treatment, normalized the FT4 (9-30 Pmol/L) levels at three weeks in 100%, and TSH (<10 mU/L) levels at six weeks in 90.5% of cases. However, hyperthyroxinaemia, FT4 levels ranging from 38 to 55 Pmol/L, was observed in six (14.3%) patients of different aetiology, which required modification in the doses given. They were initially started on higher dosages (12.3 – 14.7 µg per kg per day). Although an empirical initial dosage of 10 – 15 µg per kg per day of L-thyroxine is adequate and rapid in normalizing the thyroid status of infants with congenital hypothyroidism detected by neonatal screening, many infants who were started on higher dosages (12.3 – 14.7) showed elevated levels of FT4 which could expose infants to a dan-gerous hyperthyroidism, therefore, an initial lower dosage of 10 – 12 µg per kg per day of L-thyroxine with frequent and close monitoring of doses, and FT4, andTSH levels is more appropriate and saver than the currently recommended dosage of 10 -15 µg per kg per day for he initial treatment of infants with congenital hypothyroidism.

Key words: L-thyroxine, thyroid stimulating hormone, Congenital hypothyroidism
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Introduction

Congenital hypothyroidism (CH) represents one of the most common preventable causes of mental retardation. Its incidence varied world-wide with Saudi Arabia being one of the highest. In the past 30 years, neonatal screening programs for CH have almost eliminated the problem of severe mental retardation previously observed in infants who were not diagnosed and treated early in infancy. The neuropsychological evaluation of children with CH detected early has shown normal mental development in most cases, although a certain percentage of infants, albeit treated early, exhibit minor anomalies of mental development. Many studies had hown that the eventual intellectual outcome depends on age at start of treatment, severity of clinical and biochemical hypothyroidism at diagnosis, bone maturation at birth, and optimal therapy. [1-17]

Although, the benefits of the screening program have been established, there are differences in opinion about the optimal dose for thyroxine replacement therapy. The initially, recommended doses of L-thyroxine, 5-7 µg per kg per day may not be sufficient subsequently, the recommendation was changed to 8-10 µg per kg per day and most recently, the American Academy of Pediatrics recommended a dose of 10-15 µg per kg per day of L-thyroxine at the start of treatment with a 50 µg tablet for infants with a T4 less than 60 nmol/L (5 µg / dl).[18-33] The lower doses of thyroxine were thought to account for the poorer outcome of some children. The larger doses in some infants caused symptoms of excessive thyroid hormone and have the potential to cause premature synostosis and delayed development.[34-6]

The objective of this study is to evaluate the efficacy in normalizing thyroid status of 10-15µg per kg per day of L-thyroxine in the initial treatment of infants with congenital hypothyroidism detected by neonatal screening in Riyadh province, Saudi Arabia.

Patients and Methods

Congenital hypothyroidism (CH) screening in Saudi Arabia is carried out in newborn babies utilizing cord blood thyroid-stimulating hormone (TSH). At the time of delivery 5cc of cord blood is collected in a sterile tube from the placental side of the cord before delivering the placenta. Plasma is then separated immediately and stored at -20°C.

TSH is then assayed on single specimens, and infants are recalled if TSH is greater than 60 mU/L, or if TSH is between 30-60 mU/L with low thyroxine (T4) of less than 80 nmol/L as by the suggested screening protocol.[7,9,11] Diagnosis is confirmed by measurements of low plasma FT4, and elevated TSH levels. Aetiological classification is made by Technetium 99m pertechnetate (99m Tc).[10].

Infants with confirmed CH, treated initially with L-thyroxine 10-15 µg per kg per day, (dosage systematically rounded to 25µg, 37.5µg and 50µg), as recommended by the American Academy of Pediatrics – Thyroid Section – Dosage adjusted thereafter based on clinical and biochemical findings.

Regular follow-up, in the Pediatric Endocrine Clinic, King Khalid University Hospital, at 3 weeks, 6 weeks, 3 months, 6 months, 9 months and one year of start of therapy, where thyroid function (FT4, and TSH) assayed each visit, and dosages were adjusted as needed.

Plasma values of FT4, and TSH measured by using the Delfia Immunoflourescent Kits (Pharmacia Diagnostic, Wallac OY, Finland). Our laboratory normal ranges were FT4 (9-25 pmol/l) and TSH (0.5-5 mU/L).

Results

The various aetiologies of CH, screening and plasma thyroid hormone levels at the time of confirmation and onset of treatment are shown in Table 1. The mean age at the time of confirmation of diagnosis and start of therapy was 13 days (range 5-38) which was similar in the three groups. Thyroid scan (Tc99m) was performed in 42 infants. The gland was ectopic in 21 (50%), athyreotic in 13 (31%), and eutopic with increased uptake in 8 (19%). There was no significant differences in the mean TSH values among the different groups in the cord and confirmation samples. Also, there was no significant differences in the mean FT4 values in the cord samples among the different groups, however, the mean FT4 values at the time of confirmation in the athyreotic group was significantly ($P<0.001$) lower than the cord blood (1.5 Pmol/L versus 8.35 Pmol/L) and that at the time of confirmation for the ectopic and eutopic group (1.5 Pmol/L versus 9 Pmol/L and 8.1 Pmol/L, respectively) which clearly indicates the transplacental transfer of thyroxine.

The mean L-thyroxine dosage at the onset of therapy was 11.3 µg per kg per day (range 9.7-14.7). This was higher in the athyreotic group, 13.5 µg per kg per day versus 11.8 µg and 10.2 µg for eutopic and ectopic groups, respectively.

Table 1. The various aetiologies of CH, mean (SD) screening of cord samples, and plasma thyroid hormone levels at the time of confirmation and start of therapy.

	Cord		Confirmation	
	TSH mU/L	**FT4Pmol/L**	**TSH mU/L**	**FT4Pmol/L**
Athyreotic n = 13 (31%)	329 (104)	8.35 (0.8)	638 (250)	1.5 (0.4)
Ectopic n = 21 (50%)	410 (142)	10 (3.1)	478 (129)	9 (4.7)
Eutopic n = 8 (19%)	308 (148)	10 (2.5)	467 (121)	8.1 (3.9)

Total = 42	366 (119)	9.5 (1.5)	526 (197)	6.5 (4.5)

Table 2a. Mean L-thyroxine dosage and plasma FT4 and TSH levels at the onset and during the period of the study in 21 patients with ectopic gland.

	Onset	3 weeks	6 weeks	3 months	6 months	9 months	12 months
L-thyroxine dosage µg per kg per day	10.2 (9.7-12.3)	8.7*	7.4	5.8	5.1	4.3	-
FT4 Pmol/L	9 (0.5-16.8)	24 (11.5-44)	19 (18-27)	23 (16-37)	21 (14-27)	23.8 (18-26)	19 (12-31)
TSH mU/L	478 (112-708)	4.8 (0.5-44)	4.5 (1.2-31)	3.7 (0.6-15)	8.2 (0.6-33)	6.7 (3.8-36)	5 (0.3 – 54)

*Dose needed to be adjusted in 2 patients due to hyperthyroxinaemia (FT4 µmol/L).

Table 2b: Mean L-thyroxine dosage and plasma FT4 and TSH levels at the onset and during the period of the study in 13 patients with athyreotic gland.

	Onset	3 weeks	6 weeks	3 months	6 months	9 months	12 months
L-thyroxine dosage µg per kg per day	13.5 (10-14.7)	9.35 *	9.1	7.8	6.7	5.3	-
FT4 Pmol/L	1.5 ± 0.4 (0.2-4)	29 (18-55)	26.1 (16-36)	23.1 (13-29)	21 (18-27)	19.1 (12-26)	18.1 (10.1-27)
TSH mU/L	638 ± 250 (408-965)	4.5 (0.8-27)	8.1 (0.3-23.5)	3.8 (0.2-15)	3.4 (0.2-12)	5 (0.6-32)	7.5 0.7-44

*Dose needed to be adjusted in 4 patients due to hyperthyroxinaemia (FT4 38-55 µmol/L)

Table 2c: Mean L-thyroxine dosage and plasma FT4 and TSH levels at the onset and during period of the study in 8 patients with eutopic gland.

	Onset	3 weeks	6 weeks	3 months	6 months	9 months	12 months

L-thyroxine dosage µg per kg per day	11.8 (10-12.5)	9.8	9.2	7.2	5.6	4.8	-
FT4 Pmol/L	8.1 ± 3.9 (0.1-11)	21 (18.6-27.8)	18 (15-27)	15.3 (14-24)	20 (16-23)	18 (15-20)	17.6 (12 – 23)
TSH mU/L	467 ± 121 (218-738)	6 (0.4-33)	5.2 (0.5-19)	1.7 (0.5-3)	3.1 (0.5-6)	5 (0.2-19)	11 (2.3 – 27)

Table 3. Dosage and thyroid function of infants who developed hyperthyroxinaemia (no. 6).

FT4 – normal 9-25 Pmol/L, TSH – normal < 10 mU/L before 1 months of age and < 5 mU/L after 1 month of age.

No.	Aetiology	Initial dosage µg/kg/day		Onset	3 weeks	6 weeks	3 months
			TSH	965	1.2	0.5	4.5
1	Athyreotic	14.7	FT4	0.8	40.5	32	26
			TSH	860	0.8	0.01	1.2
2	Athyreotic	12.5	FT4	1.8	55	38	23
			TSH	930	0.6	13	1.2
3	Athyreotic	13.5	FT4	2.8	38	24	26
			TSH	680	0.23	0.9	1.3
4	Athyreotic	12.8	FT4	2.5	45	34	27
			TSH	208	0.05	0.6	1.7
5	Ectopic	13.1	FT4	16.8	44	25.8	24
			TSH	112	1.5	3.6	1.2
6	Ectopic	12.3	FT4	12.5	43.6	22.5	25
			TSH	625.8 (375.2)	0.7 (0.6)	3.1 (5)	1.9 (1.3)
	Total Mean (SD)	13.2 (0.9)	FT4	6.2 (6.7)	44.4 (5.8)	29.4 (6.2)	25.2 (1.5)

N.B. All patients' dosages was reduced (25%) at 3 weeks.

The mean L-thyroxine dosage was then decreased gradually by age as their weight increased. Tables 2a, b and c showed the evolution of mean L-thyroxine dosage and plasma thyroid hormone levels during the study period. Thyroid hor-mone levels increased rapidly and FT4 levels was normalized at three weeks in 100% of patients and TSH (less than 10 mU/L) levels at six weeks in 90.5% of cases. Hyperthyroxinaemia, FT4 levels ranging from 38 to 55 Pmol/L was observed in six (14.3%) patients of different aetiology (Table 3). They were initially started on relatively higher dosage (12.3 – 14.7 µg per kg per day) and needed to be adjusted at 3 weeks.

Discussion

The percentage of various aetiologies of CH found in this study are in accordance with those generally observed [9-11]. As expected, athyreotic infants showed more profound hypothyroidism manifested by higher TSH and lower FT4 levels.

Our prospective study clearly shows the great variability in response in the majority of treated infants. Variations in absorption, catabolism and endogenous production of thyroxine in patients with ectopic and eutopic glands as compared with athyreotic patients have been suggested [34]. The currently recommended protocol i.e. an initial higher dosage of 10-15µg/kg/day, suggested by the American Academy of Paediatrics [18] clearly induced rapid normalization of FT4 and TSH levels in the majority of treated infants. However, this also induced hyperthyroxinaemia in majority of patients treated with an initial dosage of more than 12 µg/kg/day, although, the majority showed normal FT4 levels, as early as three weeks. This means that with such higher dosages of L-thyroxine patients would probably be subjected to abnormally high levels of FT4 and therefore, at risk of the deleterious effect of hyperthyroidism, hence, the development of craniosynostosis and developmental delay [13,15,33-36].

TSH levels could remain abnormal for many months even though plasma thyroid hormone levels are in the normal range. This could be explained by, a greater need for thyroid hormone in newborn infants, or immaturity of TSH-thyroid hormone feedback regulation. There is a negative correlation between TSH and plasma FT4 levels but the concentration of plasma thyroxine at which TSH secretion becomes normal change with age, and is particularly high, during the first weeks of life [20-25, 27,29,37].

Although TSH levels may be indicative of the biological efficacy of circulating thyroid hormone, we don't know whether a slightly raised TSH values is really associated with the risk of any long term adverse effect and perhaps this is an indication to keep plasma thyroid hormone values at the upper limit of the normal range but not in the superiorly high levels. [31,37].

In conclusion, although an empirical initial dosage of 10-15 µg per kg per day of L-thyroxine is adequate and rapid in normalizing the thyroid status of infants with CH detected by neonatal screening, many infants who were started on higher dosages (12.3-14.7 µg/kg/day), showed elevated levels ofFT4 which could expose infants to a dangerous hyper-thyroidism, and have the potential to cause premature synostosis and delayed development, therefore, an initial lower dosage of 10-12 µg/kg/day of L-thyroxine with fre-quent and close monitoring of doses, and FT4 and TSH levels is more appropriate and saver than the currently recommended dosage of 10-15 µg/kg/day for the initial treatment of infants with congenital hypothyroidism.

Abbreviations:
CH – Congenital Hypothyroidism
99mTc- Technetium 99m pertechnetate
TSH- Thyroid Stimulating Hormone
FT4 – Free Thyroxine

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