Comparison between Liquid and Tablet Formulations of Levothyroxine in the Initial Treatment of Congenital Hypothyroidism

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Objective To evaluate the effects of liquid (drops) and tablet formulations of levothyroxine in homogeneous groups of infants with congenital hypothyroidism (CH) as diagnosed through neonatal screening.

Study design Forty-two consecutive infants with CH were subdivided into 2 groups consisting of infants with the severe or the moderate/mild form. For each form, the infants with CH were randomly assigned to receive liquid (group 1) or tablet (group 2) formulation. In all patients, thyroid function tests were performed before the beginning of therapy and at 15 and 30 days and at 3 and 6 months after the beginning of therapy.

Results In the severe form, after 15 days of treatment, serum thyrotropin (TSH) levels became normal in 8 of 9 patients in group 1 and in 5 of 9 patients in group 2; serum free triiodothyronine (fT3) levels were significantly higher in group 1 than in group 2; and serum fT4 levels were higher than the upper limit of the normal range in all patients in both groups. During the follow-up, there were significantly more patients with suppressed TSH concentrations in group 1 than in group 2. In the moderate/mild form, the patients of group 1 and group 2 showed median values of TSH, fT3, and fT4 that were not significantly different. No clinical or electrocardiographic signs of heart disease were found. There were no significant differences in the developmental quotient between group 1 and group 2 patients with severe and moderate/mild CH.

Conclusions Our data seem to indicate that there is not complete bioequivalence between drops and tablets, especially in infants with severe CH. *(J Pediatr 2013;162:1264-9)*.

An initial daily dose of 10-15 μg/kg levothyroxine (L-T4) in tablet form according to prenatal severity of congenital hypothyroidism (CH) has been recommended in the US and Europe.[1,2] Recently, a liquid formulation (drops) was approved by the US Food and Drug Administration and it has been licensed in Europe (Tirosint Drops, IBSA, Lugano, Switzerland). The oral solution allows a more accurate daily dose titration that may be useful for the treatment of newborns and infants with CH.

The comparative bioavailability of the 2 different formulations has been studied in adult volunteers.[3] However, the method used to assess the bioequivalence has been found to be inadequate to meet the clinical needs of patients with hypothyroidism.[4,5]

The therapeutic equivalence of the tablets and the liquid has been evaluated only in adults with acquired hypothyroidism.[6] To our knowledge, there are no comparative studies on the effects of the initial dose of liquid and tablet formulation in the treatment of infants with CH detected through neonatal screening.[7]

Two studies evaluating the follow-up of infants with CH treated with the liquid formulation showed discordant results and do not provide conclusive results.[8,9] Touati et al[8] suggest that an initial dosage of 8 μg/kg/d L-T4 may be appropriate for the majority of infants, but they also admit that the solution used in their study was unstable, thus allowing a different concentration over time. On the other hand, Van Heppe et al[9] conclude that an initial dosage in the range of 12-15 μg/kg/d (comparable with the recommended dose in tablet form) is needed to quickly achieve the normalization of thyrotropin (TSH) and free thyroxine (fT4) levels.

The liquid formulations currently available in Europe contain ethanol as an excipient. There are no data on the possible side effects related to the use of this substance in neonates.

Therefore, we evaluated, in a pilot prospective study, the clinical, hormonal, and psychodevelopmental outcomes over a 6-month follow-up in a sample of infants with CH subdivided into those with the severe form and those with the moderate/mild form and randomly assigned to receive treatment with drops or tablets.

CH	Congenital hypothyroidism
DQ	Developmental quotient
fT3	Free triiodothyronine
fT4	Free thyroxine
L-T4	Levothyroxine
TSH	Thyrotropin

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Methods

Sixty-two consecutive infants with CH diagnosed through neonatal screening at our center between June 2008 and May 2011 were considered for the present study. Exclusion criteria were gestational age <37 weeks, low or very low birth weight, congenital heart defects, serious medical illnesses, maternal thyroid diseases, and substances/disorders interfering with the absorption of L-T4.[7] Twenty infants were excluded: 4 infants were born prematurely, 6 had a positive history for maternal thyroid disease, 2 had multiple congenital malformation, 4 had parents who refused consent, and 4 were lost to follow-up after the first examination. Therefore, 42 infants (25 girls and 17 boys) were enrolled in the study with parental consent. The study was approved by the ethical committee of our hospital.

The patients were subdivided into 2 groups: severe and moderate/mild forms of CH. This distinction was made according to bone maturation at birth as evaluated through radiographic assessment of the distal femoral epiphyseal ossification center at the confirmation of the diagnosis (severe CH: bony nucleus absent or its diameter <3 mm; moderate/mild CH: bony nucleus diameter ≥3 mm).[10,11] The etiologic classification and the thyroid measures at the beginning of the treatment in patients with different CH forms are reported in Table I.

The initial L-T4 dose was chosen according to the prenatal severity of the disease: 12-13.5 μg/kg/d in infants with severe CH and 10-11.5 μg/kg/d in infants with moderate/mild CH.[1,2,7]

Before starting treatment, the infants with CH, for each form (severe and moderate/mild), were randomly assigned to receive the liquid (group 1) or tablet (group 2) formulation (stratified randomization). Infants receiving the tablet formulation received the same initial dose of L-T4 as did those receiving the liquid formulation. One drop of liquid formulation contains 3.57 μg of sodium L-T4 and the liquid solution contains 28.8 vol% of ethanol (1 mL = 243 mg ethanol) as an excipient. The mean initial dosage was 12.8 ± 0.5 μg/kg/d (ie, 30.9 mg/kg of ethanol in the liquid formulation) for those with the severe form and 10.5 ± 0.6 μg/kg/d (ie, 24.9 mg/kg of ethanol in the liquid formulation) in those with the moderate/mild form. Parents were given uniform instructions on the daily fasting administration of both formulations and on the interval between the liquid or tablet therapy and food administration.

The patients with CH were examined in a longitudinal study before the beginning of the therapy, after 15 and 30 days of treatment, and then at 3 and 6 months of age (Tables II and III).

The L-T4 dosage was adjusted in an attempt to keep the serum TSH within the normal range and the free thyroid hormone concentrations within the upper limit of the normal range. The latter was defined according to the range criteria adopted in our laboratory, depending on the patient's age.[12]

Clinical signs of hyperthyroidism and hypothyroidism were evaluated in all patients at each examination, growth measures and pulse were recorded, electrocardiography was performed, and blood samples were taken to determine TSH and free thyroid hormone serum levels.

Serum free thyroid hormone and TSH levels were measured with use of a commercial chemiluminescent assay (Bayer, Fenwald, Germany) (normal ranges: TSH 0.5-5 mU/L, free triiodothyronine (fT3) 3.1-7.7 pmol/L, fT4 10.5-22 pmol/L).

At 6 months of age, the infants with CH underwent a psychomotor evaluation with use of the Griffiths' Mental Development Scales-R for children aged 0-2 years.[13] A developmental quotient (DQ) of 100 is considered to be the mean score of normally developing infants. Mild developmental delay was defined as a DQ score between 68 and 84 (1-2 SDs below the mean), and severe developmental delay was defined as a DQ of >2 SDs below average (DQ ≤ 68). The examiner was the same for all the subjects and was unaware of the patients' treatment assignment.

Statistical Analyses

The statistical analysis was performed using SPSS (SPSS Inc, Chicago, Illinois). Results were expressed as median and range (lowest and highest value for each data point). A nonparametric statistical analysis was adopted given the small amount of available data. All comparisons between the 2 subgroups in each CH form were performed using the Mann-Whitney *U* test. Categorical data were analyzed with use of the χ^2 or Fisher exact test as appropriate. *P* values <.05 were considered statistically significant.

Table I. Thyroid measures at diagnosis in patients with CH

	Sex, girls/boys	No. of patients	TSH, mU/L	fT3, pmol/L	fT4, pmol/L
Severe CH	16/2	18	618.55	2.61	3.15
Athyreosis	5/1	6	642.40	1.92	2.64
Ectopia	9/1	10	581.45	2.76	4.31
In situ gland	2/0	2 (Goiter)	357.2	3.00	3.02
Moderate/mild CH	9/15	24	45.41	7.07	14.55
Athyreosis	—	—	—	—	—
Ectopia	2/2	4	79.01	6.07	15.13
In situ gland	6/14	20	40.18	7.07	14.16

Table II. Thyroid hormone values and therapeutic dose in infants with severe CH form at each examination

	No. of patients	Chronologic age, d	TSH, μU/mL	fT3, pmol/L	fT4, pmol/L	Dosage, μg/kg/d
Before therapy						
Group 1	9	14 (10-18)	623.2 (442.4-931.5)	2.8 (1.8-4.3)	3.6 (2.2-6.3)	12.6 (12.0-13.5)
Group 2	9	12 (9-22)	597.7 (228.4-1000)	2.6 (1.7-3.8)	2.9 (1.8-6.3)	12.9 (12.2-13.6)
15 d after therapy						
Group 1	9	29 (24-31)	1.5 (0.6-5.9)	9.5 (6.9-12.3)*	38.0 (33.3-50.7)	10.1 (9.2-12.5)
Group 2	9	29 (23-36)	2.0 (0.4-11.5)	6.4 (6.0-9.5)	29.9 (25.7-42.0)	10.6 (5.2-11.8)
30 d after therapy						
Group 1	9	60 (38-64)	0.2 (0.04-3.0)	8.1 (5.8-10.9)	27.5 (24.3-44.7)	8.3 (5.8-9.4)
Group 2	9	58 (50-66)	0.6 (0.04-7.6)	7.1 (5.7-8.4)	29.2 (20.8-35.1)	7.8 (6.7-9.9)
3 mo after therapy						
Group 1	9	126 (93-141)	0.2 (0.02-7.6)	7.4 (5.07-9.4)	23.7 (17.1-37.5)	4.7 (3.6-9.2)
Group 2	9	130 (113-172)	0.5 (0.02-6.8)	6.4 (6.0-9.5)	22.4 (18.8-42.1)	5.6 (3.8-7.4)
6 mo after therapy						
Group 1	9	228 (159-262)	0.3 (0.02-5.7)	7.2 (6.0-8.1)	21.0 (18.9-26.9)	3.5 (2.0-6.8)
Group 2	9	235 (193-288)	3.0 (0.02-7.5)	6.6 (4.0-7.7)	21.5 (18.9-27.6)	4.1 (2.6-6.3)

The range in parentheses represents the lowest and the highest values.
*$P = .0001$ versus group 2.

Results

Severe CH Forms

Growth (length, weight, and head circumference) was in the normal range in both groups. No clinical or electrocardiographic signs of heart disease were found in any patient. After 15 days of treatment, symptoms of insomnia and restlessness were reported in 1 patient in group 1 and in 3 patients in group 2.

TSH. After 15 days of treatment, serum TSH levels became <5 mU/L in 8 of 9 patients in group 1 and in 5 of 9 patients in group 2. No TSH value was below the lower limit of the normal range. During the subsequent follow-up, there were significantly more patients with TSH concentrations <0.5 mU/L in group 1 than in group 2 (12 of 27 [44% examinations in group 1] vs 4 of 27 [15% examinations in group 2]; $P = .037$).

fT3. After 15 days of treatment, the patients of group 1, compared with those of group 2, showed significantly higher median values of fT3 ($P = .0001$) (Table II). The serum fT3 levels were higher than the upper limit of the normal range in 6 of 9 subjects in group 1 and in 2 of 9 subjects in group 2 (7 of 8 patients were found among the subjects with residual thyroid tissue). Despite progressive reductions in the dosage, these levels remained abnormally elevated until the following examination at 3 months in 3 patients in group 1 and in 1 patient in group 2 (Figure 1; available at www.jpeds.com).

fT4. After 15 days of treatment, serum fT4 levels were higher than the upper limit of the normal range in all patients in both groups. The serum fT4 levels progressively decreased in both groups, but they remained higher than the upper limit until the last examination in 4 patients in group 1 and in 2 patients in group 2 (Figure 1).

Dose. During the follow-up, at least one adjustment of the therapeutic dosage (according to the appearance of biochemical and/or clinical signs of hyperthyroidism or hypothyroidism) was needed in 9 of 9 patients in group 1 and in 8 of 9 patients in group 2 (reduction in the dose in 90% of the patients in group 1 and in 65% of the patients in group 2).

Table III. Thyroid hormone values and therapeutic dose in infants with moderate/mild CH form at each examination

	No. of patients	Chronologic age,d	TSH, μU/mL	fT3, pmol/L	fT4, pmol/L	Dosage, μg/kg/d
Before therapy						
Group 1	11	14 (8-17)	44.3 (21.9-370.4)	6.9 (4.3-7.5)	13.9 (6.8-20.2)	10.3 (10.0-11.9)
Group 2	13	15 (8-23)	46.5 (15.3-152)	7.2 (4.9-8.9)	14.9 (7.2-18.3)	10.7(10.0-11.7)
15 d after therapy						
Group 1	11	28 (23-30)	0.47(0.07-6.8)	7.5 (5.5-11.5)	30.6 (16.6-40.5)	8.4 (6.8-9.4)
Group 2	13	32 (23-37)	0.41(0.09-4.6)	7.4 (6.0-8.9)	26.8 (20.7-38.4)	8.7 (6.7-10.4)
30 d after therapy						
Group 1	11	58 (36-66)	0.1 (0.03-11.9)	7.5 (6.1-8.9)	28.3 (18.0-32.7)	6.0 (4.8-8.6)
Group 2	13	60 (45-79)	0.5 (0.02-10.8)	6.6 (5.4-8.6)	23.8 (19.4-33.7)	6.2 (4.7-9.3)
3 mo after therapy						
Group 1	11	121 (99-160)	0.7 (0.02-3.4)	6.8 (5.8-7.9)	22.1 (19.7-26.5)	4.3 (2.7-7.7)
Group 2	13	133 (108-144)	0.7 (0.02-7.4)	6.4 (5.8-8.6)	20.3 (15.9-23.5)	4.4 (2.9-6.7)
6 mo after therapy						
Group 1	11	225 (200-330)	0.6 (0.02-13.2)	6.6 (5.53-7.8)	19.6 (13.6-23.6)	3.0 (2.0-6.3)
Group 2	13	243 (194-323)	1.9 (0.26-15.7)	6.0 (5.07-8.4)	18.7 (14.5-20.7)	3.3 (2.4-6.2)

Table IV. Global DQ and its subscales at 6 months in patients with severe and moderate/mild CH of groups 1 and 2

	DQ	Locomotor	Social	Hearing and speech	Eye-hand coordination	Performance
Severe CH (N = 13)	96					
Group 1 (n = 7)	96 (77-119)	93 (72-119)	89 (75-127)	100 (88-132)	104 (79-127)	91 (62-106)
Group 2 (n = 6)	98 (83-111)	96 (73-112)	92 (80-117)	98 (73-114)	107 (79-123)	98 (77-112)
Moderate/mild CH (N = 19)	103					
Group 1 (n = 9)	103 (87-110)	93 (78-115)	108 (87-117)	109 (87-124)	109 (87-117)	91 (84-101)
Group 2 (n = 10)	102 (94-113)	102 (87-117)	109 (89-115)	106 (84-120)	109 (84-122)	97 (68-117)

Moderate/Mild CH Form

Growth (length, weight, and head circumference) was in the normal range in both groups. No clinical or electrocardiographic signs of heart disease were found in any patient. After 15 days of treatment, symptoms of insomnia and restlessness have been reported in 3 patients in group 1 and in 2 patients in group 2.

TSH. After 15 days of treatment, serum TSH levels became <5 mU/L in 10 of 11 patients in group 1 and in 13 of 13 patients in group 2. TSH values below the lower limit of the normal range were found in 5 patients in both groups. During the subsequent follow-up, the percentage of patients with TSH concentrations below 0.5 mU/L was not significantly different in group 1 and in group 2 (13 of 33 [39% of examinations in group 1] vs 9 of 39 [23% of examinations in group 2]).

fT3. After 15 days of treatment, serum fT3 levels were higher than the upper limit of the normal range in 5 of 11 patients in group 1 and in 2 of 13 patients in group 2 (nonsignificant). The fT3 concentrations normalized in all patients in both groups after 1 or 3 months of treatment (**Figure 2**; available at www.jpeds.com).

fT4. After 15 days of treatment, serum fT4 levels were higher than the upper limit of the normal range in 9 of 11 patients in group 1 and in 12 of 13 patients in group 2. The serum fT4 levels progressively decreased in both groups, and they became normal in all patients after 6 and 3 months of treatment, respectively, in group 1 and in group 2 (**Figure 2**).

Dose. During the follow-up, at least one adjustment of the therapeutic dose (according to the appearance of biochemical and/or clinical signs of hyperthyroidism or hypothyroidism) was needed in 11 of 11 patients in group 1 and in 11 of 13 patients in group 2 (reduction in the dose in 63% of the patients in both groups).

Psychomotor Development

The global DQ and its subscales at 6 months are shown in **Table IV**. DQ values <84 were observed only in 2 infants with severe CH and poor socioeducational level (1 infant in group 1 and 1 infant in group 2).

Discussion

With both of the formulations, the recommended initial doses tailored according to CH severity normalized the TSH levels and restored the thyroid function in practically all the patients at the first examination after beginning treatment. However, despite careful adjustments, the median levels of fT4 remained above the upper limit of the normal range for age for several months. Moreover, in many patients, serum concentrations of fT3, the active hormone with the main metabolic effects, were above the physiologic levels with persistently suppressed levels of TSH. This pattern was more evident in the patients with severe CH presenting a residual thyroid tissue with varying endogenous production of thyroxine that were treated with higher doses of the liquid formulation.

The appropriate initial dose of L-T4 that is necessary to achieve the optimal outcome in infants with CH detected by neonatal screening remains controversial. At present, there is no sufficient evidence from randomized controlled trials to evaluate the effectiveness of high- versus low-dose regimens.[14,15] The results of the present study do not solve this; however, even though preliminary, they do not seem to support the effectiveness of the highest doses. All our patients, treated with both formulations, showed fT4 levels higher than the upper limit of the normal range for many months. Moreover, some of them also showed high fT3 levels during the first months of treatment, at variance with previous literature data. This could lead us to assume that the L-T4 doses that are currently recommended in international guidelines are too high.

The availability of liquid formulations introduces another treatment variable potentially influencing the short-term follow-up in the first months of life.[7,16] We were not able to formally assess parental satisfaction by questionnaire, but some data reported in literature confirm that the liquid formula is easier to administer and the dosage is easier to adjust for each individual: for this reason, this kind of formula has been welcomed by parents and physicians.[9] However, the possible side effects and the differences in the absorption and bioavailability related to the different formulations have not been adequately studied.

Our data seem to indicate an incomplete bioequivalence between the liquid and the tablet preparations, especially in infants with severe CH. The liquid formula is apparently easier for parents to handle, so some mistakes in the administration

(eg, number of drops administered, volume of the mixed liquid) cannot be excluded. On the other hand, the observed pattern appears to be rather uniform and not limited to just a few patients characterized by a poor social and/or educational background. Moreover, we cannot exclude that the more frequent suppression of TSH observed in group 1 actually signifies that the liquid form is more efficacious than the tablet, which has to be crushed, undergoing a process that might cause some loss of the drug.

Although preliminary, our results seem to partially agree with the data of both Touati et al[8] and Van Heppe et al.[9] The initial higher dosages recommended in international guidelines can be applied even to the subjects treated with the liquid formulation, although not in a systematic way. The systematic treatment with these doses, in fact, may expose some infants to a high risk of overdosage with long-term behavioral effects.[17-19]

Initial doses not higher than 10 μg/kg/d seem adequate to obtain a quick normalization of the thyroid measures, even in some infants with severe CH showing a greater residual thyroid function. Nonetheless, close monitoring and more frequent examinations during the first months of treatment are needed to carefully adjust the dosage at the individual level and to avoid the risk of overtreatment.[20]

Regarding cardiac evaluation, pulse rate, recorded at each examination, was found to be in the normal range for age (sometimes in the upper limit). It is difficult, at the moment, to explain these results, even if they confirm that thyroid hormone serum levels are not always the expression of the thyroid function at the tissue level, especially in infancy.

On the one hand, these data are reassuring about the treatment's short-term safety; on the other hand, they do not exempt us from careful monitoring of the adequacy of dosage. In fact, long-term detrimental cardiac effects related to overtreatment are reported.[21]

Regarding the use of ethanol as an excipient, there are no clinical studies in the literature on the possible detrimental effects in neonates. The only available studies about the consumption of ethanol are those carried on during pregnancy and lactation. These studies,[22-24] which indirectly estimated the fetal/neonatal exposure to ethanol, showed that the consumption of a daily dose up to 75 mg is not associated with short- or long-term detrimental effects on the infant. It is also important to note that ethanol is normally eliminated from the blood circulation very quickly (in ~3 hours). In our study, the growth and the psychometric outcomes seem to be in the normal range in all the subjects treated with the liquid formulation. This seems to be true also for some patients with severe CH, who took daily doses >75 mg, at least during the first days of treatment. We did not measure in our patients surrogate markers of liver function to further support the safety of the ethanol content of the liquid formulation. However, careful monitoring of possible side effects from ethanol consumption is mandatory because these patients, unlike those reported in literature, will have to consume ethanol for a long time.

The findings of DQ evaluated at 6 months should be considered preliminary. The randomization in such a small sample of subjects has probably prevented the recruitment of well-matched groups with respect to social, economic, and educational conditions. Despite these limits, our results seem to show similar outcomes among the subjects treated with the different solutions.

It is also important to note that the DQ in the patients with severe CH seems to be lower than that in the patients with moderate/mild forms, although the treatment has been conducted early with high dosages in all patients. This result can be partly explained by a selection bias, induced with the 2 subjects with a poor parental social and educational level in the severe form group. On the other hand, the presence of unavoidable factors of prenatal severity, as pointed out by Dimitropoulos et al,[25] cannot be excluded.

The present study was meant as a pilot exploratory study. It should have been able to evaluate possible differences in the short-term outcome of a homogeneous, although small, sample of patients enrolled in a single center, but no firm conclusions can be drawn from our findings. We believe that these results can be used to properly plan and realize a randomized multicenter trial with adequate sample size and with a demonstrative aim. ■

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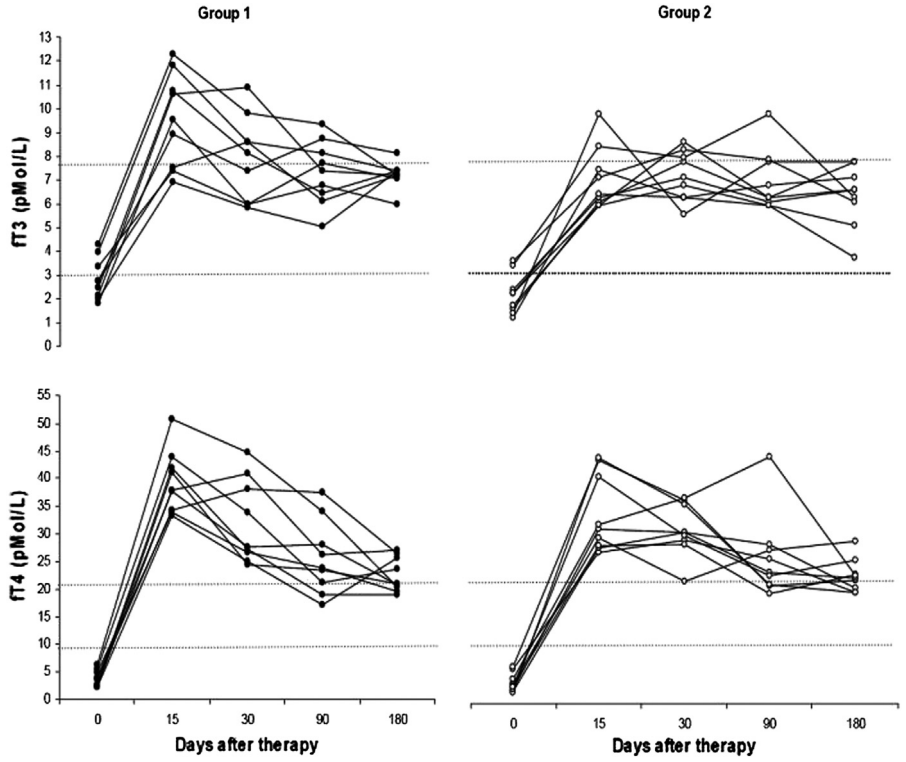

Figure 1. Thyroid hormone levels and therapeutic dose in severe CH forms.

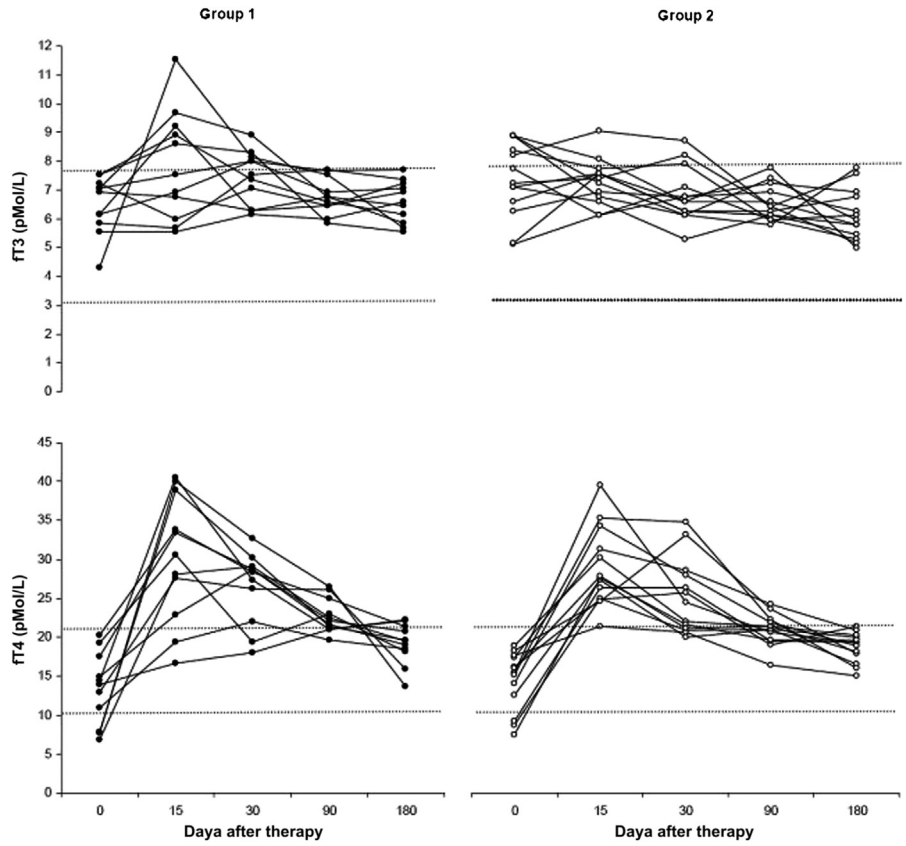

Figure 2. Thyroid hormone levels and therapeutic dose in moderate/mild CH forms.

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