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