A Double-Blind Placebo-Controlled Trial of Liquid Thyroxine Ingested at Breakfast: Results of the TICO study

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ABSTRACT:

Background:

Levothyroxine (L-T4) is the recommended treatment for millions of hypothyroid patients. Current guidelines recommend that L-T4 tablets be taken in a fasting state, but inability to adhere to this often leads to poor therapy compliance.

Methods:

We conducted a randomized, double-blind, placebo-controlled, crossover trial in previously untreated hypothyroid patients randomly assigned to receive an oral solution of L-T4 either at least 30 minutes before breakfast or directly at breakfast time. Each patient completed two 6-week treatment periods, with different timing of active L-T4 administration: placebo before breakfast and active L-T4 at breakfast, or vice versa. At the end of each period, TSH, fT4 and fT3 were measured. The primary endpoint was to verify any difference in serum TSH levels whether consuming liquid L-T4 at breakfast or 30 minutes prior to breakfast.

Results:

A total of 77 patients (64/13 female/male, median age 45.4 ±13.7) completed the study. No statistically significant difference of serum TSH, fT4 and fT3 levels was observed whether L-T4 was taken at breakfast or 30 minutes before, in a fasting state.

No significant effect from the sequence of regimens, breakfast composition and/or concomitantly administered drugs was observed on the dose of L-T4 administered, or on the post-treatment serum TSH values.

Conclusions:

The TICO study suggests that a liquid L-T4 formulation can be ingested directly at breakfast, thus potentially improving therapeutic compliance. This observation is of considerable clinical relevance, since non-adherence to L-T4therapy requirements is more likely to cause variability in serum TSH concentrations.

INTRODUCTION:

Hypothyroidism is one of the most common chronic disorders worldwide, with prevalences ranging from 0.1 to 2 percent of the population (1-3). Levothyroxine (L-T4) is the treatment of choice and a serum TSH concentration maintained within a narrow range represents the best marker of successful treatment (4,5). The management of hypothyroidism is generally considered straightforward even though cross-sectional surveys of patients taking levothyroxine demonstrate that between 40% and 48% are either over-treated or under-treated (2,6).

Different factors may interfere with intestinal absorption of L-T4, including food ingestion, dietary fibre, coffee, drugs, gastric or intestinal resection and diseases, and current guidelines recommend that L-T4 should be taken in a fasting state (4,7).

On the other hand, adherence to medical recommendations has been recognized as challenging, especially with regard to drug therapy (8), and a significant number of patients have difficulty complying with L-T4 therapy as they have to postpone their breakfast by 30-60 minutes (9). Over the last few years new, non-tablet L-T4 formulations, such as liquid and soft gel capsules, have been introduced in some countries. Recently, we serendipitously identified hypothyroid patients who maintained euthyroidism despite taking liquid L-T4 contrary to guidelines at breakfast, with their coffee; when the same patients started to ingest the same dose of liquid L-T4 as recommended at least thirty minutes before breakfast, no changes of TSH, free T4 and free T3 values were observed (10). To further prospectively evaluate the efficacy of oral liquid L-T4 administration at breakfast, we conducted the TICO study (*TIroxina a COlazione*, translated as "Thyroxine at Breakfast"): a double-blind, placebo-controlled trial, involving naïve hypothyroid patients starting replacement therapy.

Materials and Methods

Study design and conduct:

The TICO study (EUDRACT registration number: 2013-001696-21) is a randomized, double-blind, placebo-controlled, crossover trial in which previously untreated hypothyroid patients were randomly assigned to receive in the morning an oral solution of L-T4 (Tirosint® fiala monouso, IBSA Farmaceutici Italia). The drug was administered either before breakfast (BEFORE), after an overnight fast and at least 30 minutes prior to food ingestion, or in a fed state directly at breakfast time (AT). The study was approved by an independent Institute Review Board and conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonisation. All the participants provided prior written informed consent.

The study was designed by the investigators and supported by IBSA Farmaceutici Italia. The pharmaceutical company prepared two identical and indistinguishable vials (labeled A and B) containing either a specified dose of L-thyroxine (25, 50, 75 or 100 µg) dissolved in 1 mL solution of 85% glycerol and 96% ethanol (243 mg) or a placebo vehicle control (1 mL of glycerol/ethanol solution).

In the morning all patients were given two vials, labeled A and B. The first vial was to be ingested after an overnight fast half an hour before breakfast diluted in a glass of water. Data indicate that gastric emptying after drinking plain water is almost complete within 30 minutes (11), so we can assume that absorption of liquid L-T4 is not influenced by food ingested 30 minutes thereafter. The second vial was ingested during each patient's usual breakfast, mixed with tea, coffee, milk, cappuccino, orange juice, etc. Each patient completed two 6-week regimens, corresponding to the sequence vial A – vial B, or vice versa, with regimens defined by the timing of active L-T4 administration: the placebo vial before breakfast and the active L-T4 vial at breakfast (regimen AT=>BEFORE), or vice versa (regimen BEFORE=>AT). Regimen sequence order was randomized according to a permuted blocks allocation scheme (1:1 ratio, with random block size of 2, 4, 6). Placebo or active drug content of vials A and B was determined by the manufacturers

at IBSA Farmaceutici and disclosed to the investigators only after study completion and blinded data analysis by the investigators.

The intake of drugs potentially interfering with L-T4 absorption (in particular iron or calcium supplements and proton pump inhibitors) was monitored and recorded. In addition, a detailed description of each subject's breakfast composition was obtained, particularly of insoluble fibers and/or soy milk. The study design is shown in Figure 1.

The authors assume responsibility for the accuracy of the data and full observance of the study protocol.

Study participants:

Patients, aged 18-75 years old, were eligible if they presented symptoms of hypothyroidism and/or TSH values above 10 mIU/L, due to Hashimoto's thyroiditis or thyroidectomy for proven benign goiter. None of the patients had received previous treatment.

Subjects with congestive heart failure (NYHA III-IV), coronary heart disease, severe hypertension, uncontrolled diabetes mellitus (HbA1c > 64 mmol/ml) or untreated dyslipidemia were excluded. In order to avoid any possible persistence of TSH elevation in the early phase of pregnancy, women who were pregnant or lactating and women who could possibly become pregnant at any time during the entire study were also excluded. All participants were required to maintain the same breakfast habits and any ongoing therapy for the full duration of the study. The introduction of any additional drugs had to be reported to the researchers.

Patient enrollment took place from October 2013 through November 2014.

The starting dose of L-T4 was determined through clinical judgment, taking into account TSH levels, estimate of residual thyroid function, age, body weight and comorbidities (4).

After the first 6-week regimen all patients were submitted to TSH, fT4 and fT3 evaluation to verify achievement of euthyroidism (0.2 ≤ TSH ≤ 4.2 mIU/L); if this was not achieved, an appropriately adjusted L-T4 dose was administered for six more weeks and thyroid function parameters re-checked afterwards.

When a euthyroid state was reached, the patients had to switch the order in which the vials were ingested and undergo treatment for a second 6-week period. Individual L-T4 doses titrated during the first sequence period did not change during the second sequence. At the end of the second sequence, measurements of TSH, fT4 and fT3 values were repeated and the study was completed. Adherence to protocol requirements (regularity and timing of taking the drugs, unchanged eating habits at breakfast) was assessed by a physician via personal interviews at the end of each regimen period. At the end of the study all patients were formally asked whether they would prefer their daily L-T4 treatment directly at breakfast or 30 to 60 minutes before.

Study endpoints

The primary endpoint was to verify any difference in serum TSH levels (and secondarily in fT4 and fT3) when **ingesting** liquid L-T4 at breakfast compared to 30 minutes earlier.

Statistical analysis, based on pilot data from patients taking L-T4 for thyroiditis, indicated that 80 subjects would provide 80% power to detect a 20% difference between TSH levels of the two regimen sequences, using a critical significance level of P=0.05. In the pilot data, a 20% difference corresponded to 0.6 mIU/L.

Hormone assays

Serum concentrations of free thyroxine (fT4; normal range: 8.0-19.0 pg/mL, analytical sensitivity 1 pg/mL), free triiodothyronine (fT3; normal range: 2.4-4.7; analytical sensitivity 0.35 pg/mL), and TSH (normal range: 0.4-4.5 mIU/L, analytical sensitivity 0.004 mIU/L) were measured using a fully automated Architect i2000 analyzer (Abbott Diagnostics, Abbott Park, IL, USA) using chemiluminescent magnetic immunoassays.

Statistical analysis

Data are presented as mean ± standard deviation for parameters with normal distribution (age, body mass index). Normal distribution was checked by the Shapiro-Wilk test. TSH, fT4 and fT3

levels resulted non-normally distributed and were not normalized by the usual procedures of data transformation; in these cases results are presented as median plus range. Comparisons between continuous variables were performed by paired samples t-test or related samples by the Wilcoxon signed rank test, as appropriate. Categorical variables were compared by the χ^2 test. A generalized linear model analysis was performed to examine the influence of potential confounders (for instance, different types of breakfast, dietary supplements or concomitantly administered drugs) on serum TSH levels.

Two-tailed $p<0.05$ was considered statistically significant. Statistical analyses were performed using SPSS 17.0 software (SPSS, Inc., Evanston, IL, USA).

RESULTS

Ninety-four patients were assessed for eligibility and 86 patients (71/15 female/male, median age 46.0±13.8 years) were eligible and enrolled in the study. Nine of 86 patients withdrew from the trial during the first sequence period: in six cases due to non-adherence to protocol requirements and in the remaining three cases for unspecified personal reasons. No patient abandoned the study over the second period of treatment, so that 77 patients (64/13 female/male, median age 45.4±13.7) completed the study. Sixty-six patients started replacement therapy for Hashimoto thyroiditis. Eleven patients started replacement therapy after thyroidectomy for the removal of histologically proven benign goiter (details are provided in Supplemental Table 1).

After data analysis and blinding disclosure, 38 patients were found to have started the regimen sequence with active L-T4 at breakfast (sequence AT=>BEFORE), while the remaining 39 patients followed the opposite sequence (BEFORE=>AT). Baseline demographic and clinical characteristics according to regimen sequence are shown in Table 1. No difference of age, sex, cause of hypothyroidism and baseline thyroid hormonal profile was observed between the two regimen sequences.

After 6 weeks of the first period of treatment, a similar number of patients (32/38, 84%, sequence AT=>BEFORE and 34/39, 87%, sequence BEFORE=>AT) achieved euthyroidism; in the subjects with TSH values still above 4.2 mIU/L, the L-T4 dose was adjusted and treatment continued for six more weeks. All these patients became ultimately euthyroid.

The median dose of L-T4 **ingested** by the 77 patients at the end of the first regimen sequence was 75 mcg daily; individual L-T4 doses titrated during the first sequence period were not changed during the second treatment period.

No difference of serum TSH, fT4 and fT3 levels was observed irrespective of whether L-T4 was ingested at breakfast or 30 minutes prior in a fasting state. The sequence of regimen (AT=>BEFORE vs BEFORE=>AT) influenced neither the dose of L-T4 administered nor the post-treatment TSH values (Table 2). Similarly, no influence of breakfast composition on TSH and thyroid hormone levels was observed in subgroup analyses, comparing subjects taking a

beverage-only breakfast (n=33) vs subjects taking solid foods in addition to beverages (n=44). We purposely did not exclude any patient on concomitant drug treatment (including proton pump inhibitors, calcium or iron supplements) or patients taking fiber and soy milk products at breakfast from the study (Supplemental Table 1). Generalized linear model analysis shows that these and other variables (age, sex, and body weight) had no significant effect on the dose of L-T4 administered or the achieved post-treatment TSH values (data not shown). No specific complaints were reported by the patients; in particular, none of the patients noticed changes in the taste of their breakfast. No adverse events were observed by the investigators. All the patients declared they would prefer to take their daily L-T4 treatment directly at breakfast.

DISCUSSION

Current guidelines for the treatment of hypothyroidism by a Task Force of the American Thyroid Association recommend that for optimal and consistent absorption levothyroxine should, if possible, be taken at least 30 minutes before breakfast (or at bedtime, at least three hours after the evening meal) (4). This recommendation is based on a small number of studies indicating that concomitant ingestion of L-T4 with food (12-15), coffee (13) or fiber and soy products (16,17) is associated with higher serum TSH values in hypothyroid subjects, compared to taking L-T4 in the fasting state. However, the Task Force acknowledges that the quality of these studies is only moderate on average and that the strength of the recommendation is weak (4).

The recent introduction of non-tablet formulations of L-T4 in the therapeutic environment seems to call this recommendation into question (18). Vita et al. (9) observed in a small number of hypothyroid patients that treatment with a soft gel preparation of L-T4 (Tiche capsules, IBSA Switzerland) is not associated with a reduced absorption of the drug by coffee (14). The same authors observed that the soft gel formulation of L-T4 can also circumvent the problem of incomplete absorption of L-T4 caused by proton pump inhibitor-induced increase of gastric pH (19).

Our group first reported on 54 patients who erroneously ingested a liquid L-T4 formulation (Tirosint, IBSA Italy) with coffee: after anticipating the time of liquid L-T4 ingestion to have been 30 minutes before breakfast, no change in TSH, fT4, and fT3 concentrations was observed (10). We have also shown that patients who have undergone bariatric surgery (bilio-pancreatic diversion) or total laryngectomy and thyroidectomy could benefit from a liquid L-T4 formulation (20), which can be administered directly through a feeding tube, with no need for an empty stomach. (21). Further, along this line of reasoning, Brancato et al. suggested that a L-T4 oral solution consumed within 1 hour before breakfast could have an increased absorption rate in comparison to L-T4 tablets, especially in the presence of other factors interfering with L-T4 absorption (22).

The main result of the present randomized, placebo-controlled, double-blind crossover trial involving patients with previously untreated acquired hypothyroidism, clearly indicates that the

administration of the same dose of oral liquid levothyroxine either at breakfast or in fasting state, 30 minutes before breakfast, has indistinguishable effects on the thyroid hormonal profile. This finding, coupled with the unanimous preference expressed by patients for taking the medication directly at breakfast, may represent a distinct advantage of the liquid L-T4 formulation compared to traditional L-T4 tablets, the absorption of which appears to be erratic when ingested together with food and/or beverages, as reported by Perez and colleagues in a recent study (15). It is widely accepted that adherence to medical recommendations, especially with regard to drug therapy, is challenging (8), and well-documented cross-sectional surveys of patients taking levothyroxine have shown that between 40% and 48% are either over-treated or under-treated (2,6). In particular, a significant number of patients find it difficult to comply with L-T4 therapy as they have to postpone their breakfast by 30-60 minutes (9).

Giusti et al. have recently reported that patients found the L-T4 tablet formulation more agreeable than liquid ones (23). We can speculate that this is partly because tablets may be easier to manage than vials, but it should also be considered that in the study by Giusti et al. the patients added liquid L-T4 to a separate glass of water, with a relatively unpleasant taste when compared to direct addition to usual breakfast beverages.

Our clinical observation with patients taking the drug mixed with coffee and other hot beverages suggests that neither high temperatures (i.e., coffee, milk, cappuccino or hot tea), nor acidity (i.e, orange juice) alter the molecular properties or stability of L-T4. Studies on stability carried out with tablet formulations have shown that sodium L-T4 rapidly degrades at 60-80°C (24,25); indeed, an Italian ‘espresso’ coffee is served at similar temperatures (26). Very recently, Bernareggi et al. have addressed this issue, demonstrating that liquid L-T4 is stable after 20 minutes in milk, tea, coffee, and cappuccino at 50°C, as well as in orange juice at room temperature (27).

One important feature of our study is that it couples a rigorous study design to a real-life approach in respect of usual breakfast habits and intake of drugs and supplements, which remained unchanged throughout the study. Actually, no influence of breakfast composition or co-treatment with other drugs (including PPI) on TSH levels was observed.

An important issue that has not been directly addressed by the present study is the question of whether liquid L-T4 may have distinct advantages over tablet preparations in terms of clinical outcomes, beyond timing of treatment. Negro et al. reported interesting data in this respect, showing that administration of a liquid L-T4 formulation compared to tablets resulted in a significantly higher number of hypothyroid patients who remained euthyroid over a 12-month follow-up, with a significant reduction of variability in TSH values (28). We have also observed in a retrospective series of 369 elderly hypothyroid patients treated with L-T4 over a five-year period that the prevalence of subclinical or overt hyperthyroidism was significantly reduced in subjects treated with liquid L-T4 compared to those treated with tablets (29). This is of particular interest in elderly patients, where the increased risk of developing heart disease, osteoporosis, bone fracture and cognitive impairment is well documented among subclinical hyperthyroid subjects (15, 30-33). The liquid formulation is currently only available in Italy. This could represent a limitation, since all the clinical studies have been conducted in this country, among people belonging to the same ethnic group, with similar breakfast habits; accordingly, further studies performed in other countries are needed.

In conclusion, the present study suggests that a liquid L-T4 formulation can be ingested directly at breakfast, thus potentially improving therapeutic compliance. This observation is of considerable clinical relevance, given that subjects who do not comply with L-T4 therapy requirements are more likely to show variability in TSH concentrations and consequent unwanted effects.

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Author Disclosure Statement

No conflicting financial interests exist.

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