Primo Congresso Interregionale
AME Sud – Italia
Matera 9 – 10 maggio 2014

FORMULAZIONI DI TIROXINA A CONFRONTO

Giuseppe Citro - Azienda Sanitaria Locale Potenza

L tiroxina cp

Valentina, nata il 25.04.1989, giunge alla prima osservazione all'età di 19 anni per sintomi suggestivi di ipertiroidismo; viene fatta diagnosi di Morbo di Basedow e trattata con antitiroidei, dapprima metimazolo, successivamente propiltiouracile, rispetto ai quali mostra una discreta resistenza, dal momento che il quadro clinico e ormonale si avvicina alla norma solo utilizzando 10 – 12 cp/die.

Non riuscendo a ridurre tale posologia, viene suggerito un intervento ablativo con I^{131}; Valentina però decide per l'intervento di tiroidectomia, che effettua nel marzo 2010.

Alla dimissione viene rivista, le si prescrive terapia con Eutirox cp con dosaggio da incrementare fino a 75 mcrg/die 30 minuti prima di colazione e con raccomandazione di ricontrollare il TSH dopo 4 settimane dal raggiungimento della posologia.

In realtà il primo controllo viene effettuato a settembre 2010 con riscontro di TSH = 87 µU/ml

L tiroxina cp

ame flash
nr. 16 - luglio 2013

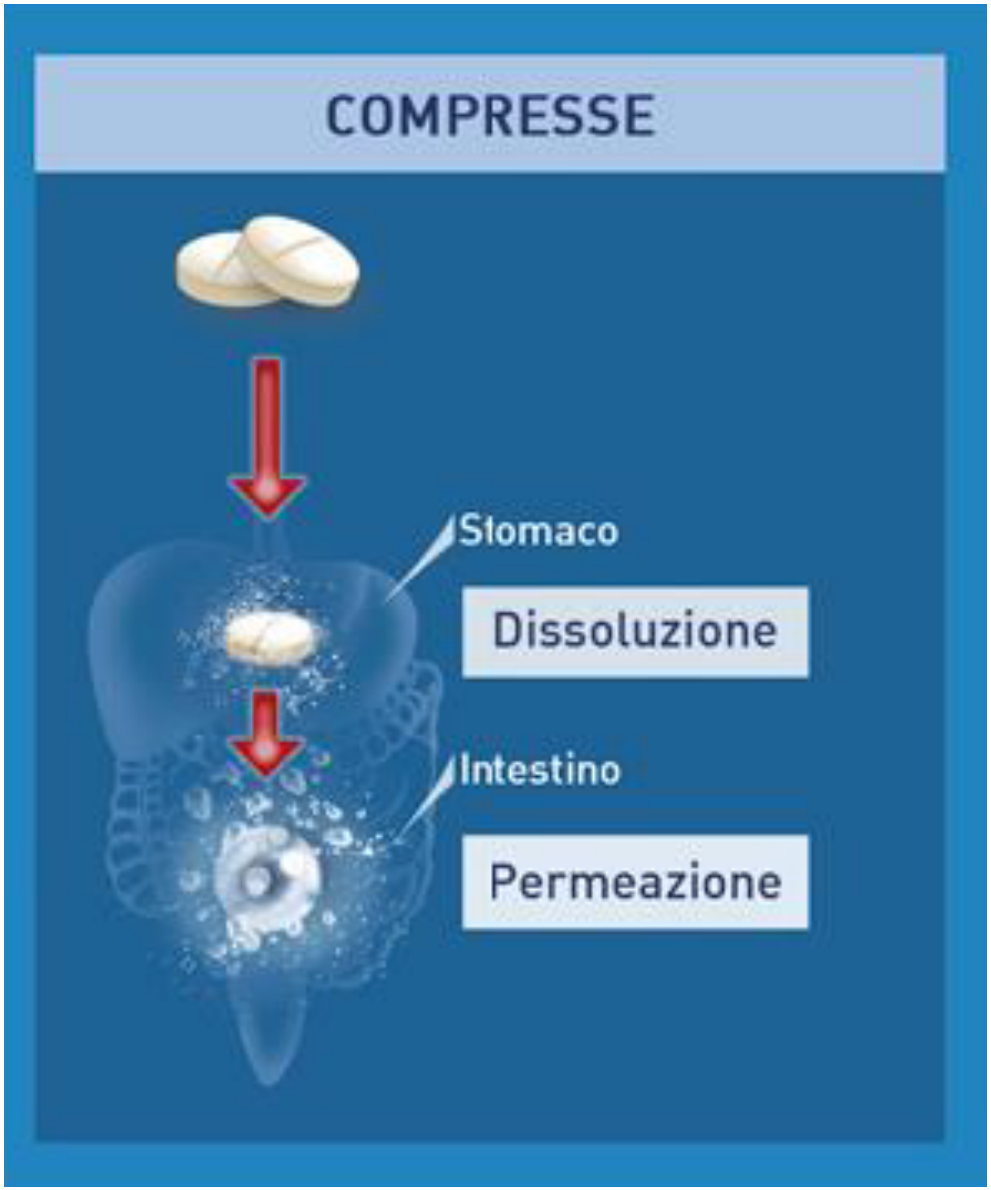
Dai dati disponibili in letteratura, il

fabbisogno medio di LT4 per mantenere normale il TSH nei pazienti ipotiroidei è 1.6 µg/Kg

European Endocrinology, 2013;9(1):40–7

For an average adult under the age of 50, the typical levothyroxine sodium dose is approximately 1.7 mcg/kg/day, which is equivalent to approximately 100–125 mcg/day. Older patients or patients with cardiac disease may require less levothyroxine and doses should be titrated at intervals of 4–6 weeks. Newborns, infants and adolescents require doses greater than 1.7 mcg/kg/day.The guidelines that were recently released by the American Association of Clinical Endocrinologists and American Thyroid Association task force on hypothyroidism in adults, in addition to diagnosis, include suggestions of therapy.

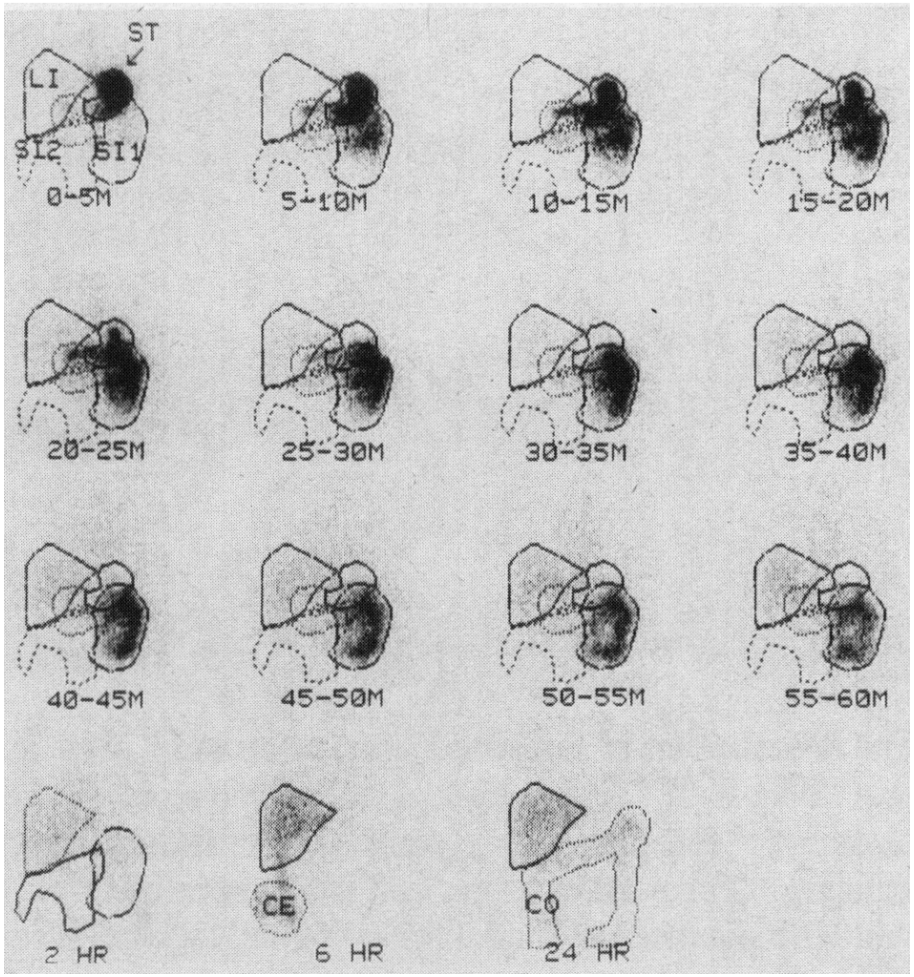
L tiroxina cp

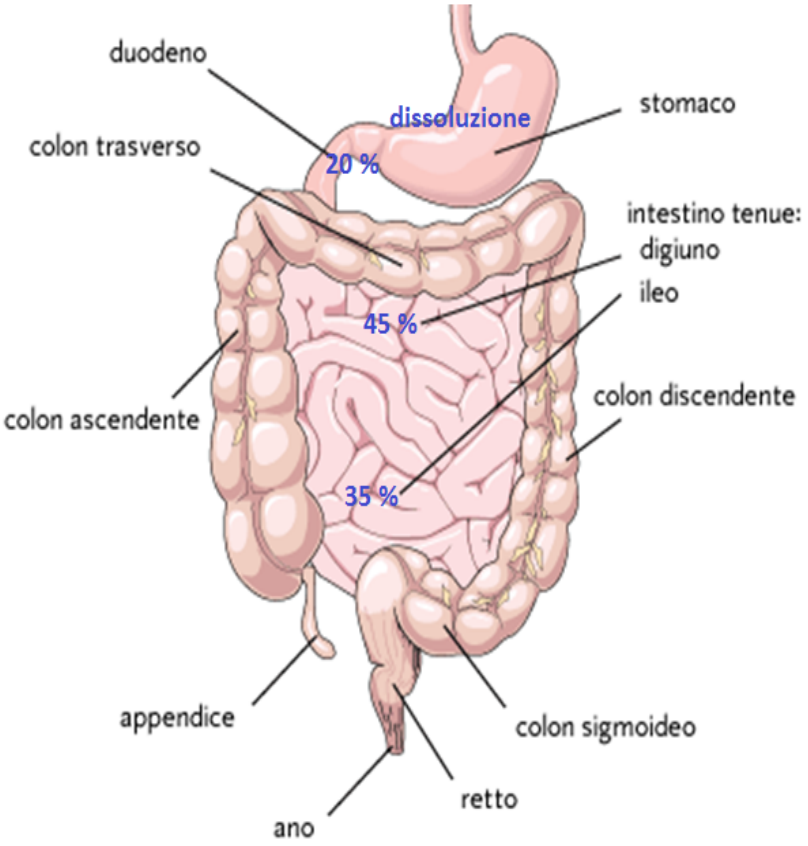


L tiroxina cp

Localization of Human Thyroxine Absorption

THYROID
Volume 1, Number 3, 1991





L tiroxina cp

Pharmacokinetic Characteristic	Description
Main site of absorption	Small intestine
Bioavailability	70–80 % in euthyroid person; may be slightly higher in hyperthyroid patients
Tmax	2–3 hours
Vd	11–15 L
Protein binding	T_4 >99.9 % T_3 = 99.8 %
T1/2	T_4 = 6.2 and 7.5 days in euthyroid and hypothyroid patients, respectively T_3 = 1.0 and 1.4 days in euthyroid and hypothyroid patients, respectively
CL	T_4 = 0.055 and 0.038 L/h in euthyroid and hypothyroid patients, respectively

Vd = Volume of distribution; L = Litres; CL = Clearance

European Endocrinology, 2013;9(1):40–7

L tiroxina cp

Pharmacokinetics of Levothyroxine in Special Populations

	Bioavail-ability	Metabolism (T_4 to T_3)	Protein Binding	Elimination	TT_4	TT_3	fT_4	fT_3
Renal impairment		↓	↓			↓		↓
Hepatic impairment (cirrhosis)		↓	↓		↑	↓	↑	↑↓
Elderly	↓	↓		↓		↓		↓
Children				↑	↓			
Obesity					↑↓	↑↓		
Pregnancy				↓			↓	
Gastrointestinal disorders	↓							
Food	↓							

↑ = *increase*; ↓ = *decrease*; ↑ ↓ = *contradiction in literature about impact. TT4 and TT3= total T4 and total T3; fT4 and fT3= free T4 and free T3.*

European Endocrinology, 2013;9(1):40–7

L tiroxina cp

Farmaci interferenti con l'effetto della Tiroxina

Sono numerosi e vanno ricordati i seguenti.

1) **Ipolipemizzanti** (colestiramina e colestipolo): riducono l'assorbimento della T4 dall'intestino al sangue; è bene far passare almeno 4-5 ore dalla loro assunzione rispetto a quella della tiroxina
2) **Anti-acidi, inibitori di pompa protonica**, preparati a base di **ferro**, farma… **alluminio**: interferiscono con la fase gastrica della tiroxina e ne possono o… a livello intestinale; per tale motivo è bene dilazionare di alm… …xina.
3) **Contraccettivi orali** o soli **estrogeni:** pos… …dell'aumento delle concentrazioni della proteina T… …ndi essere necessario adottare degli aggiustamen… …zione.
4) **Anti-ep**… …ale): accelerano il catabolismo epatico della tiroxina …do, potenzialmente, di ridurne l'efficacia.
5) **I**… …sse modalità degli anti-epilettici.
6) **A**… **…panololo:** possono ritardare il catabolismo della tiroxina a livello epatico, prolungandone l'e… …nel tempo.
7) **L'anti-depressivo sertralina e gli anti-malarici clorochina e proguanile:** riducono l'efficacia della levotiroxina e aumentano il livello sierico del TSH.

Interferenze della Tiroxina sulla farmacocinetica di altri farmaci

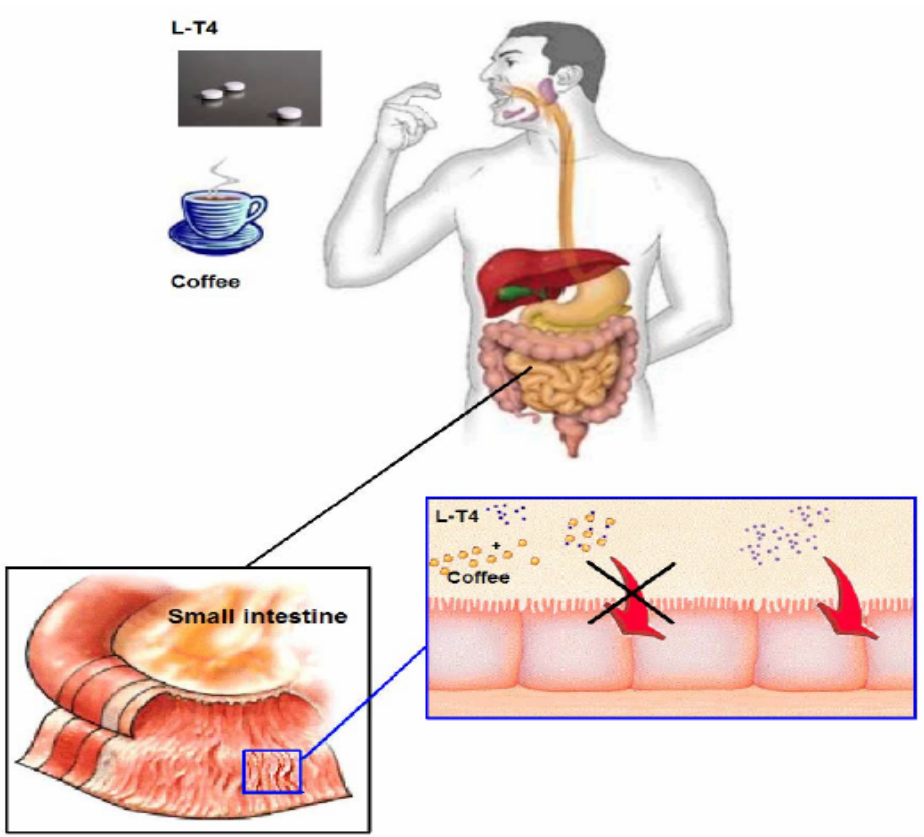
1) **Derivati cumarinici:** la levotiroxina può aumentare l'azione dei derivati cumarinici a causa della competizione di legame per l'albumina sierica. In concomitanza di trattamento è necessario monitorare regolarmente i fattori della coagulazione, abbassando eventualmente il dosaggio dell'anti-coagulante.

Interferenze nutrizionali	Alimenti a base di soia
	Assunzione di fibre

L tiroxina cp

Hut Thyroidology

Article # 05/09



Sequestering activity of coffee reduces intestinal absorption of L-T4.

L tiroxina cp

THYROID
Volume 18, Number 3, 2008

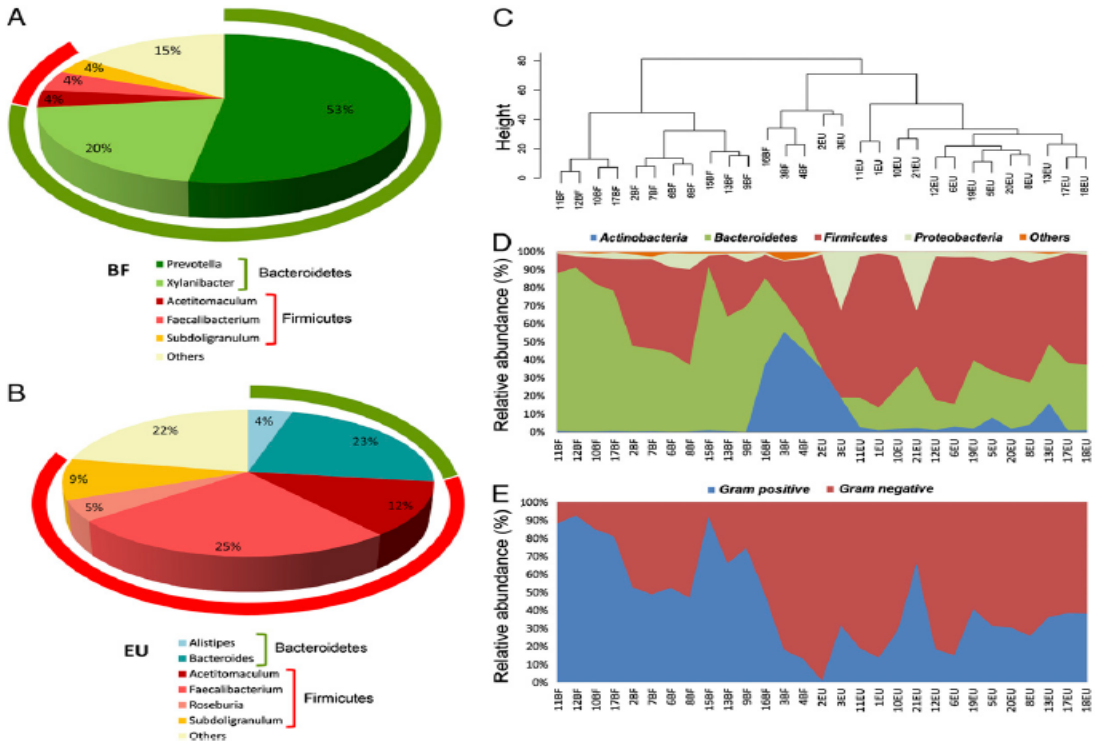
Salvatore Benvenga, Luigi Bartolone, Maria Angela Pappalardo, Antonia Russo, Daniela Lapa, Grazia Giorgianni, Giovanna Saraceno, and Francesco Trimarchi

INDICES OF T4 ABSORPTION IN THE ACUTE LOADING TEST OF 200 μG ORAL L-T4 IN FOUR DIFFERENT MODALITIES OF INGESTION OF T4 BASED ON THE FLUID USED TO SWALLOW THE L-T4 TABLETS[a]

		Patients (n = 6)				*Volunteers no. 1–4, 6–10 (n = 9)*				*Volunteer no. 5 (n = 1)*			
		Average (nmol/L)	*Peak (nmol/L)*	*Peak (minutes)*	*AUC (nmol/[L · 4 hours])*	*Average (nmol/L)*	*Peak (nmol/L)*	*Peak (minutes)*	*AUC (nmol/[L · 4 hours])*	*Average (nmol/L)*	*Peak (nmol/L)*	*Peak (minutes)*	*AUC (nmol/[L · 4 hours])*
Water alone	Mean ±SD	36.3 ±16.7	51.8 ±11.9	130 ±41	8696 ±1590	35.4 ±14.9	48.4 ±8.4	120 ±47	8304 ±1900	10.5 ±7.0	17; 19 N/A	120; 120 N/A	2565; 2745 N/A
Espresso	Mean ±SD *p*-value	23.0 ±12.7 < 0.0001	36.0 ±8.8 < 0.05	180 ±38 < 0.05	5592 ±1452 < 0.05	25.1 ±14.1 < 0.0001	39.4 ±7.1 < 0.05	163 ±67 0.068	6038 ±1356 < 0.01	19.7 ±10.4 < 0.01	33; 28 N/A	90; 120 N/A	4860; 4365 N/A
Water (espresso 1 hour later)	Mean ±SD *p*-value	36.2 ±16.1 0.86 (NS)	52.0 ±8.5 0.53 (NS)	125 ±44 0.56 (NS)	8622 ±1481 0.40 (NS)	35.3 ±15.9 0.95 (NS)	43.2 ±3.6 0.26 (NS)	127 ±51 0.57 (NS)	8358 ±1944 0.95 (NS)	11.3 ±8.8 0.52 (NS)	22 N/A	120 N/A	2490 N/A
Bran[b]	Mean ±SD *p*-value	7.0 ±7.3 < 0.01	20; 7 N/A	180; 180 N/A	2715; 900 N/A	8.9 ±7.2 < 0.01	10; 21 N/A	240; 120 N/A	1515; 2985 N/A	Not done	Not done	Not done	Not done
Aluminum hydroxide	Mean ±SD *p*-value	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done	3.2 ±2.9 < 0.05	7 N/A	240 N/A	792 N/A

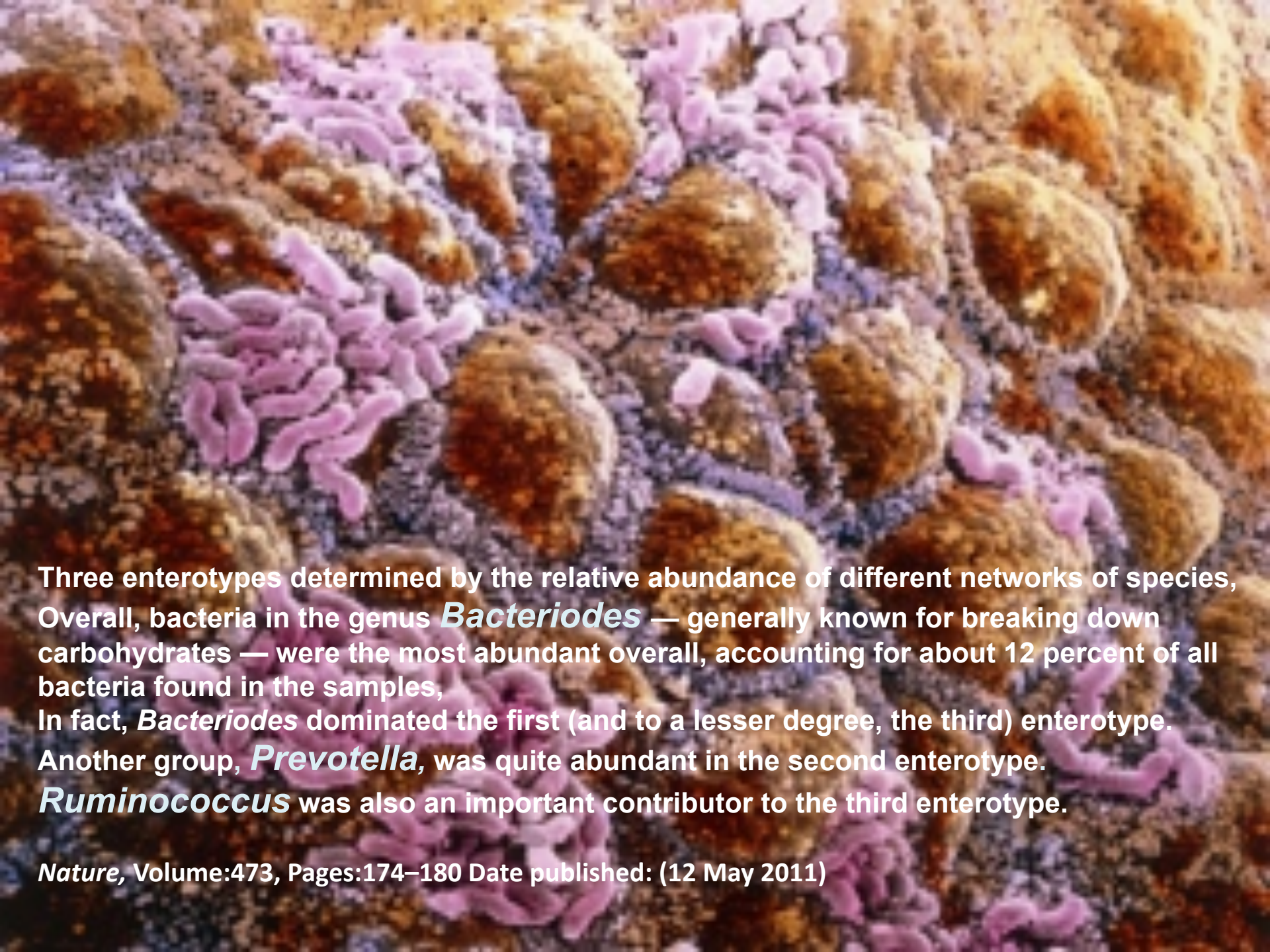
[a]Statistical analysis (vs. water alone) is by Wilcoxon signed rank sum test for paired data.
[b]Bran refers to patients no. 1 and 2, and volunteers no. 1 and 2. In the two patients, the four tabulated values for water alone were 32.7 ± 11.8, 42 and 45, 120 and 180, and 7350 and 8145. In the two volunteers, the four tabulated values for water alone were 32.8 ± 9.8, 44 and 41, 120 and 120, and 7830 and 7515. In a comparison between bran and espresso, 7.0 ± 7.3 was different from 23.2 ± 12.9 ($p < 0.01$) in patients no. 1 and 2, and 8.9 ± 7.2 was different from 22.8 ± 16.7 ($p < 0.01$) in volunteers no. 1 and 2. Numbers in brackets are daily doses of L-T4 in μg/kg body weight.
T4: thyroxine; L-T4: levothyroxine; AUC: area under the curve; N/A: not applicable; NS: not significant.

L tiroxina cp



16S rRNA gene surveys reveal a clear separation of two children populations investigated. (*A* and *B*) Pie charts of median values of bacterial genera present in fecal samples of BF and EU children (>3%) found by RDP classifier v. 2.1. Rings represent corresponding phylum (Bacteroidetes in green and Firmicutes in red) for each of the most frequently represented genera. (*C*) Dendrogram obtained with complete linkage hierarchical clustering of the samples from BF and EU populations based on their genera. The subcluster located in the middle of the tree contains samples taken from the three youngest (1–2 y old) children of the BF group (16BF, 3BF, and 4BF) and two 1-y-old children of the EU group (2EU and 3EU). (*D*) Relative abundances (percentage of sequences) of the four most abundant bacterial phyla in each individual among the BF and EU children. Blue area in middle shows abundance of Actinobacteria, mainly represented by *Bifidobacterium* genus, in the five youngest EU and BF children. (*E*) Relative abundance (percentage of sequences) of Gram-negative and Gram-positive bacteria in each individual. Different distributions of Gram-negative and Gram-positive in the BF and EU populations reflect differences in the two most represented phyla, Bacteroidetes and Firmicutes.

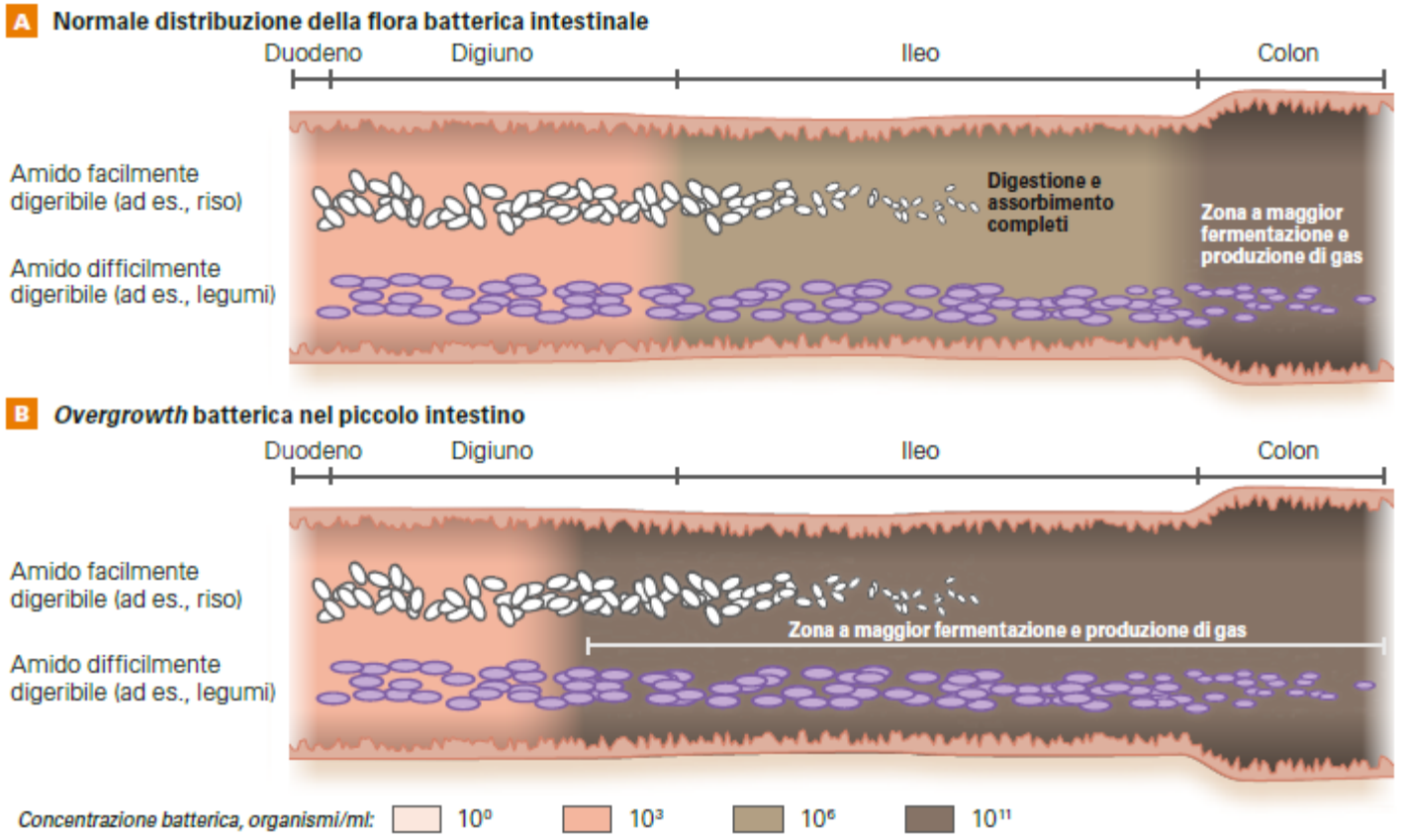
Proc Natl Acad Sci U S A. 2010 Aug 17;107(33):14691-6



Three enterotypes determined by the relative abundance of different networks of species,
Overall, bacteria in the genus *Bacteriodes* — generally known for breaking down carbohydrates — were the most abundant overall, accounting for about 12 percent of all bacteria found in the samples,
In fact, *Bacteriodes* dominated the first (and to a lesser degree, the third) enterotype.
Another group, *Prevotella,* was quite abundant in the second enterotype.
Ruminococcus was also an important contributor to the third enterotype.

Nature, Volume:473, Pages:174–180 Date published: (12 May 2011)

L tiroxina cp



L'*overgrowth* intestinale batterica è molto frequente nei soggetti ipotiroidei, a causa di un'alterazione della motilità del colon che favorisce la migrazione verso l'alto dei batteri : in questi soggetti il dosaggio di levo tiroxina, fortemente metabolizzata da questi batteri, può aumentare notevolmente.

L tiroxina cp

Timing of Levothyroxine Administration Affects Serum Thyrotropin Concentration

Thien-Giang Bach-Huynh, Bindu Nayak, Jennifer Loh, Steven Soldin, and Jacqueline Jonklaas

Division of Endocrinology (T.-G.B.-H., B.N., J.L., S.S., J.J.), and Bioanalytic Core Laboratory, General Clinical Research Center (S.S.), Georgetown University Medical Center, Washington, D.C. 20007

J Clin Endocrinol Metab 94: 3905–3912, 2009

LT_4 timing regimens, sequences, and time periods used in the study

	LT_4 timing sequences A–F					
Time period	A	B	C	D	E	F
Weeks 1–8	BB	HS	WB	WB	BB	HS
Weeks 9–16	HS	WB	BB	HS	WB	BB
Weeks 17–24	WB	BB	HS	BB	HS	WB

LT_4 timing regimens: BB, WB, and HS.

L tiroxina cp

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J Clin Endocrinol Metab 94: 3905–3912, 2009

Effect of timing of LT_4 ingestion (fasting, with breakfast, or at bedtime) on the arithmetic mean of thyroid analytes (TSH, FT_4, T_3) for hypothyroid patients and patients with thyroid cancer

Analyte	BL	BB	WB	HS
Hypothyroid patients				
Mean TSH, mIU/liter (SD)	1.77 (1.20)	1.54 (1.27)	3.74 (3.55)	2.79 (2.15)
Mean FT_4, ng/dl (SD)	1.20 (0.23)	1.23 (0.22)	1.16 (0.22)	1.2 (0.25)
Mean T_3, ng/dl (SD)	128 (24)	125 (33)	121 (25)	123 (24)
Thyroid cancer patients				
Mean TSH, mIU/liter (SD)	0.29 (0.50)	0.27 (0.58)	1.41 (2.02)	1.14 (3.12)
Mean FT_4, ng/dl (SD)	1.45 (0.30)	1.57 (0.28)	1.39 (0.24)	1.50 (0.28)
Mean T_3, ng/dl (SD)	136 (29)	134 (32)	127 (28)	129 (29)

SI conversions: to convert FT_4 to picomoles per liter, multiply by 12.871; and to convert T_3 to nanomoles per liter, multiply by 0.0154. BL, Baseline.

L tiroxina cp

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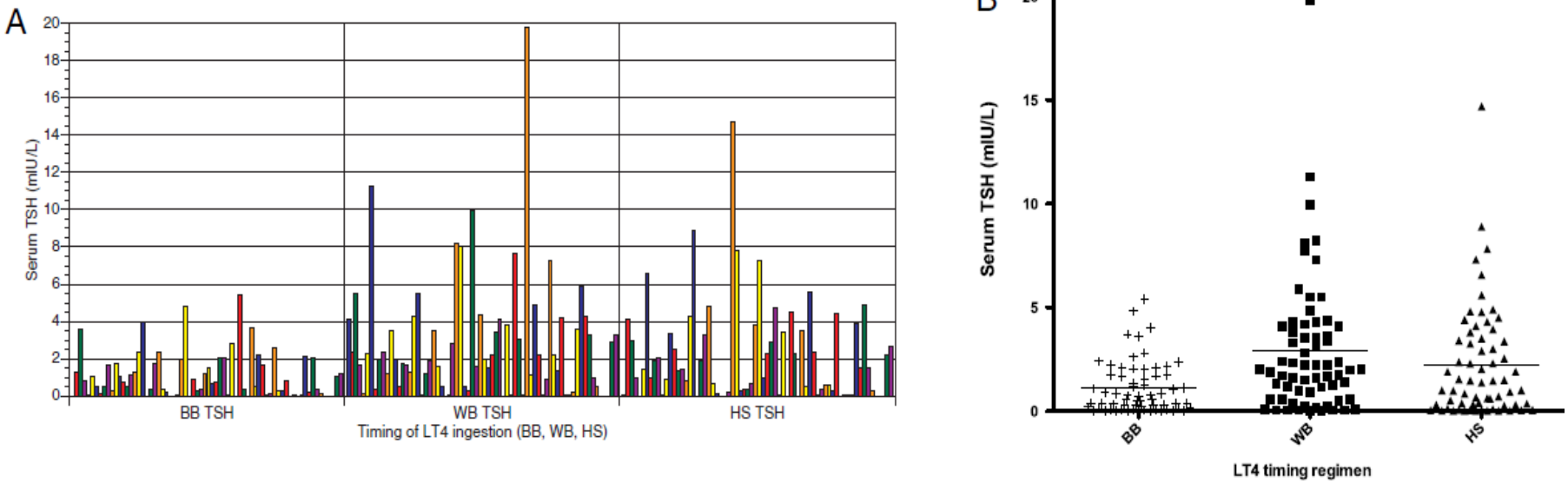

A, Serum TSH concentrations of participants according to their LT_4 timing regimen (fasting, with breakfast, or at bedtime) for subjects who completed the study. Patients are displayed in the order and the *same color* in each of the three levothyroxine timings (each patient is not a unique color). B, Scatter plot showing TSH values during each LT_4 timing regimen for subjects who completed the study.

L tiroxina cp

Timing of Levothyroxine Administration Affects Serum Thyrotropin Concentration

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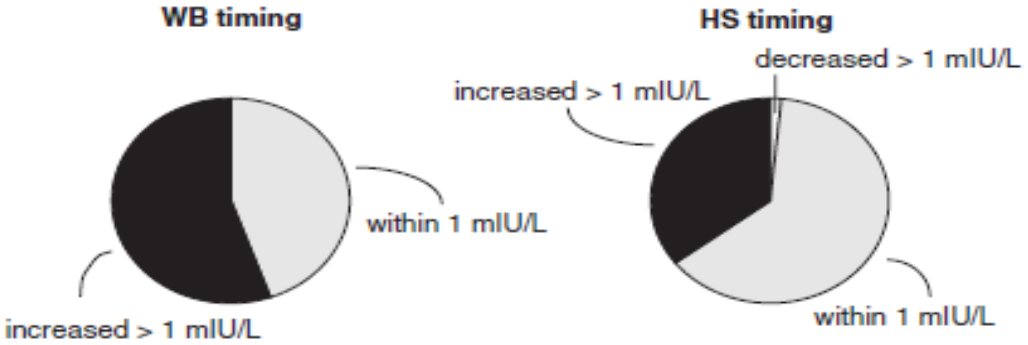


Change in serum TSH between a fasting regimen and either a WB regimen (*left sided chart*) or HS regimen (*right sided chart*). Pie chart showing percentage of patients whose serum TSH level decreased by more than 1 mIU/liter (*white*), remained within 1 mIU/liter (*gray*), and increased by more than 1 mIU/liter (*black*) when changing from a fasting regimen to a WB regimen and from a fasting regimen to an HS regimen.

L tiroxina cp

Valentina, pesa 65 kg

Viene aumentato il dosaggio a 100 mcrg/die)

Le si richiede di assumere la cp 1 ora prima di colazione evitando in quel lasso di tempo di assumere anche il caffè e/o qualsiasi farmaco (raccomandazione inutile perchè Valentina non assume caffè e non prende farmaci)

Viene effettuato un controllo dopo 40 giorni con riscontro di TSH = 113 µU/ml

L tiroxina cp

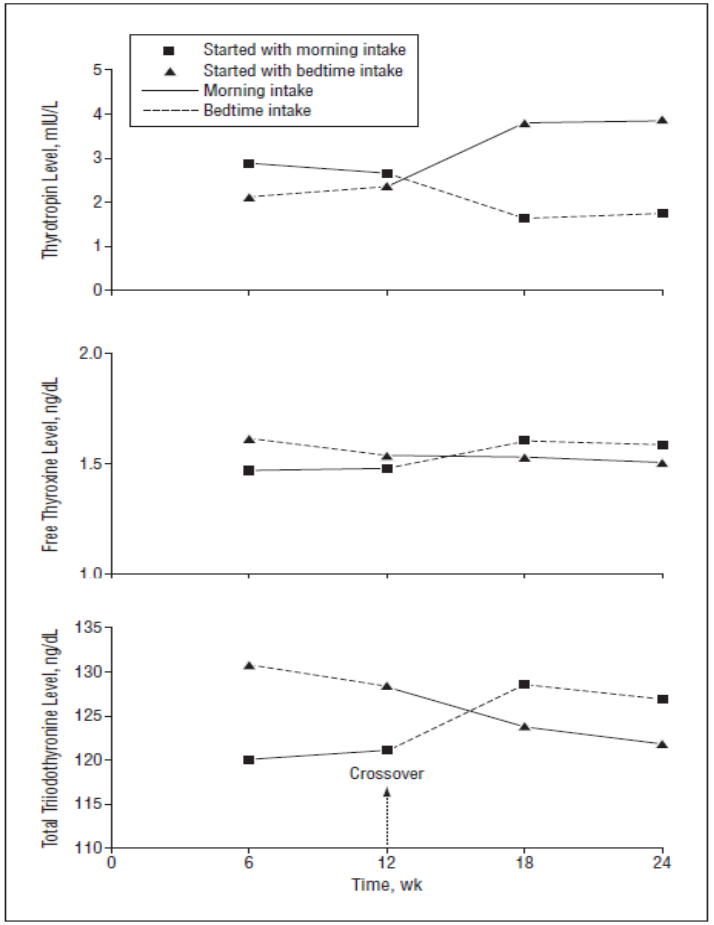
Effects of Evening vs Morning Levothyroxine Intake

A Randomized Double-blind Crossover Trial

Nienke Bolk, MD; Theo J. Visser, PhD; Judy Nijman, BSc; Ineke J. Jongste, RN; Jan G. P. Tijssen, PhD; Arie Berghout, MD, PhD, FRCP

ARCH INTERN MED/ VOL 170 (NO. 22), DEC 13/27, 2010

Methods: To ascertain if levothyroxine intake at bedtime instead of in the morning improves thyroid hormone levels, a randomized double-blind crossover trial was performed between April 1, 2007, and November 30, 2008, among 105 consecutive patients with primary hypothyroidism at Maasstad Hospital Rotterdam in the Netherlands. Patients were instructed during 6 months to take 1 capsule in the morning and 1 capsule at bedtime (one containing levothyroxine and the other a placebo), with a switch after 3 months. Primary outcome measures were thyroid hormone levels; secondary outcome measures were creatinine and lipid levels, body mass index, heart rate, and quality of life.



Thyroid hormone levels after 6 and 12 weeks of morning or bedtime intake of levothyroxine sodium. To convert thyrotropin level to micrograms per liter, multiply by 1.0; free thyroxine level to picomoles per liter, multiply by 12.871; and total triiodothyronine level to nanomoles per liter, multiply by 0.0154.

L tiroxina cp

Can Levothyroxine Be Taken as Evening Dose? Comparative Evaluation of Morning versus Evening Dose of Levothyroxine in Treatment of Hypothyroidism

Rajesh Rajput, Sumanto Chatterjee, and Meena Rajput

Comparison of biochemical parameters (data expressed as mean ± SD) of Group 1 and Group 2 at the end of 6 and 12 wks.

Biochemical parameter	Group 1			Group 2		
	Baseline	6 wks	12 wks	Baseline	6 wks	12 wks
fT3 (pg/mL)	2.09 ± 1.03	2.91 ± .75 ($P < .0001$)	3.48 ± 1.09 ($P < .0001$)	2.15 ± 1.03	2.93 ± 1.01 ($P < .0001$)	3.20 ± 0.54 ($P < .0001$)
fT4 (ng/dL)	0.72 ± 0.59	1.31 ± 0.45 ($P < .0001$)	1.5 ± 0.33 ($P < .0001$)	0.74 ± 0.5	1.30 ± 0.49 ($P < .0001$)	1.48 ± 0.31 ($P < .0001$)
TSH (mIU/L)	82.79 ± 56.32	17.03 ± 18.33 ($P < .0001$)	5.13 ± 9.36 ($P < .0001$)	78.23 ± 43.15	12.64 ± 44.27 ($P < .0001$)	3.27 ± 4.19 ($P < .0001$)
Triglyceride (mg/dL)	158.50 ± 89.36	141.17 ± 62.4 ($P = .08$)	141.10 ± 62.76 ($P = .08$)	158.75 ± 89.72	149.82 ± 78.07 ($P = .50$)	137.24 ± 68.37 ($P = .09$)
Cholesterol (mg/dL)	194.95 ± 63.21	182.19 ± 44.27 ($P = .48$)	177.66 ± 39.71 ($P = .012$)	196.88 ± 75.69	176.64 ± 38.35 ($P = .029$)	173.85 ± 38.25 ($P = .015$)
HDL (mg/dL)	43.25 ± 20.76	39.88 ± 6 ($P = .14$)	44.36 ± 15.74 ($P = .311$)	42.84 ± 12.91	41.56 ± 12.91 ($P = .54$)	43.29 ± 12.14 ($P = .88$)
LDL (mg/dL)	119.44 ± 48.08	112.88 ± 34.48 ($P = .29$)	108.59 ± 33.45 ($P = .56$)	113.06 ± 40.05	105.79 ± 29.85 ($P = .27$)	103.68 ± 31.27 ($P = .65$)
VLDL (mg/dL)	30.86 ± 17.79	29.19 ± 14.11 ($P = .19$)	28.31 ± 13.13 ($P = .34$)	31.54 ± 15.80	29.20 ± 12.69 ($P = .13$)	27.44 ± 15.33 ($P = .76$)

Journal of Thyroid Research
Volume 2011, Article ID 505239, 5 pages

152 drug naïve primary hypothyroid patients were divided into morning (Group 1) and evening (Group 2) dosing group and evaluated for change in biochemical profile, physical functioning and Quality of Life during the course of 12 weeks of study. At the end of 12 weeks 70 (90.90%) subjects in Group 1 and 72 (96%) in Group 2 achieved euthyroidism. On evaluation clinical symptoms and total clinical scores improved in both the groups at the end of 6 and 12 weeks. Significant improvement in thyroid profile was seen in both the groups at the end of 6 and 12 weeks (P value <.0001). On intergroup comparison, no significant difference in thyroid profile was seen at 6 and 12 weeks between the morning and the evening dose group. Similar dose of levothyroxine was required to achieve euthyroidism in both the groups. Though an early restoration of euthyroidism was seen in evening group, the difference when compared to the morning group was not statistically significant. On assessment of QoL, statistically significant improvement in various parameters was seen in both the groups. Hence, from the study we inferred that evening dose is as efficacious as morning dose and provides an alternate dosing regimen.

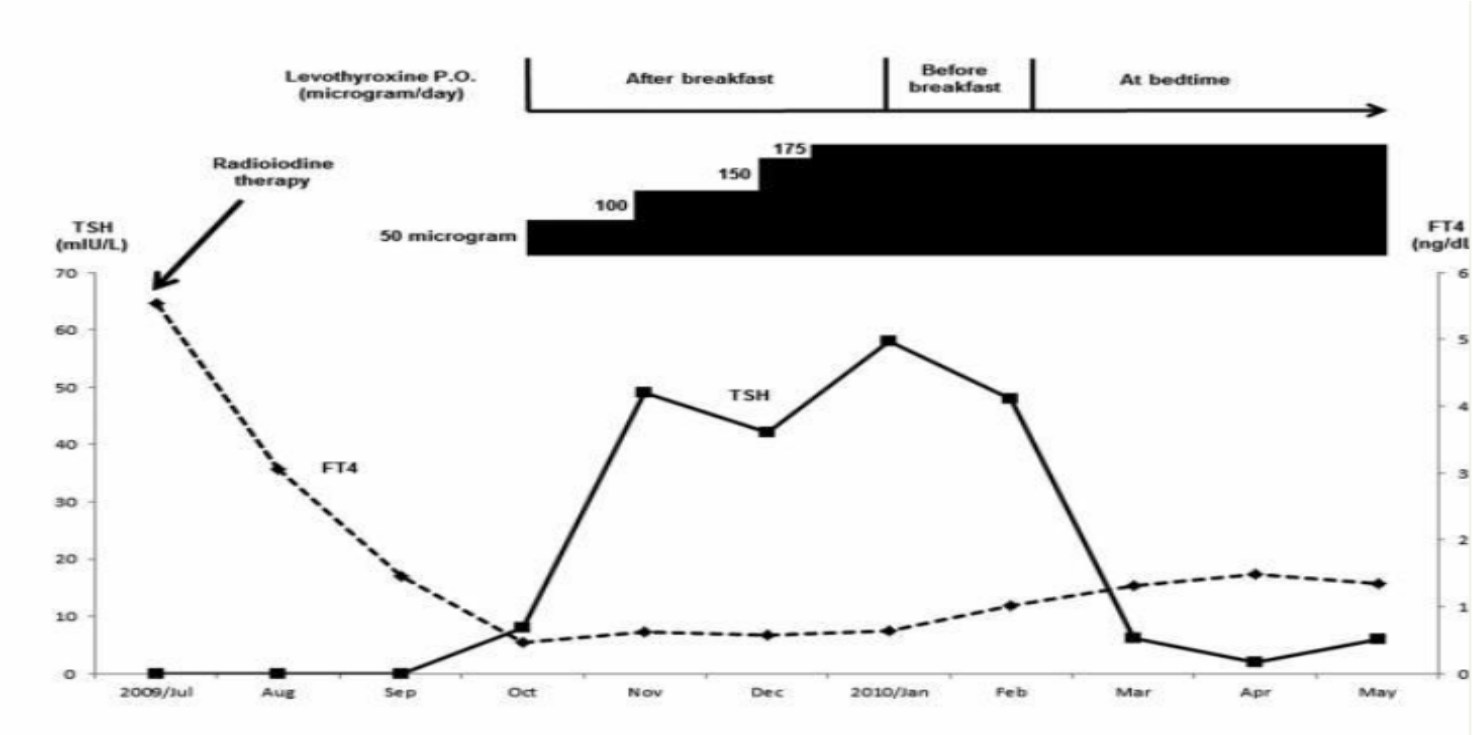
L tiroxina cp

Case Report

Journal of Endocrinology and Metabolism.

Volume 2, Number 6, December 2012, pages 232-234

Marked Improvement of Levothyroxine Malabsorption by Simply Changing the Timing of Thyroxine Ingestion in an Adult Woman With Hypothyroidism After Radioiodine Therapy for Graves' Disease



La presenza di cibo e/o l'incremento del pH gastrico

Foods	Medical conditions	Drugs
Food intake	Jejunoileal bypass or other bowel resection	Cholestyramine
Dietary fiber SOIA	Inflammatory bowel disease	Colesevelam
Espresso coffee	Celiac disease	Ferrous sulfate
	Lactose intolerance	Sucralfate
	H. pylori infection	Calcium carbonate
	Chronic gastritis of the stomach body	Aluminum hydroxide
		Sevelamer hydrochloride
		Lanthanum carbonate
		Raloxifene
		Proton pump inhibitors
		Orlistat

Anche gli eccipienti possono avere un effetto interferente

quando essa non è ancora completamente in soluzione,

interferendo con l'assorbimento.

L tiroxina cp

Valentina ha un TSH di 113 µU/ml, riferisce astenia, sensazione di gonfiore, sonnolenza continua nell'arco della giornata

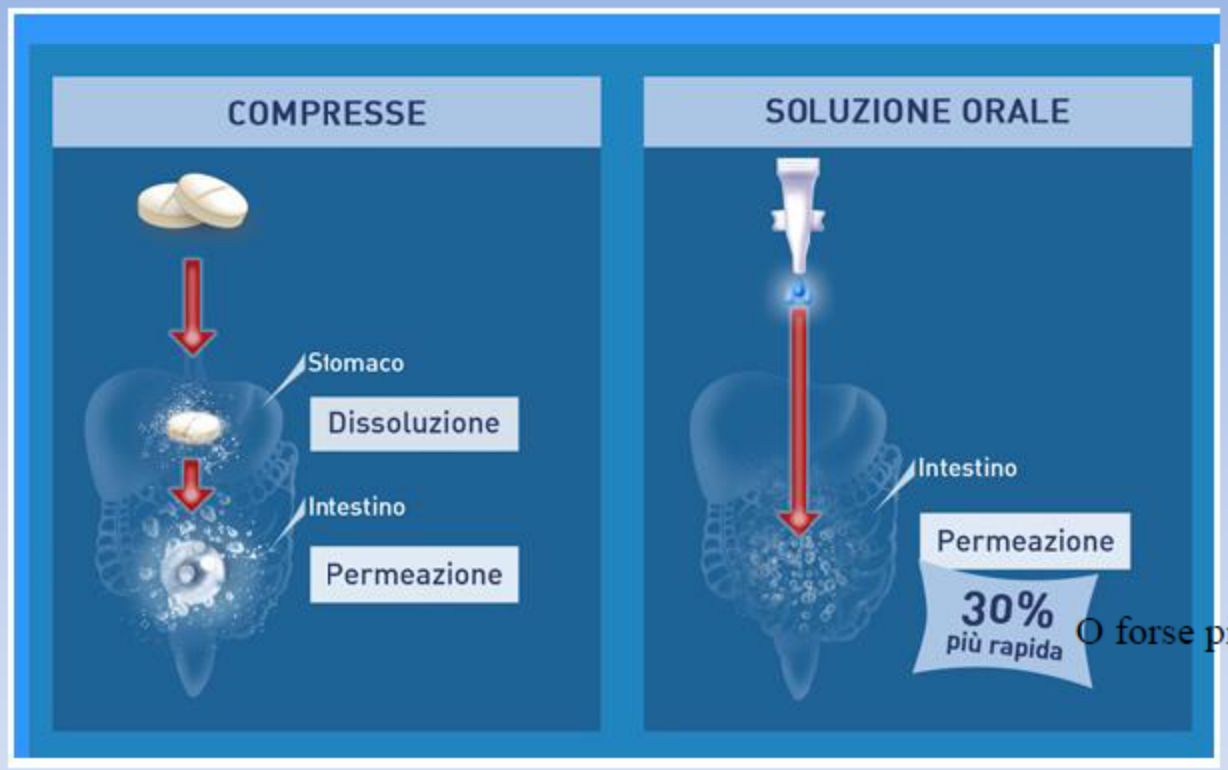
Viene sostituito Eutirox cp con Tirosint cp

Viene aumentato ulteriormente il dosaggio fino a 125 mcrg/die)

Le si richiede di cenare alle 19 e assumere la cp 3 ore dopo cena

Viene effettuato un controllo dopo 40 giorni con riscontro di TSH = 210 µU/ml

L tiroxina liquida



L'assorbimento delle formulazioni liquide è un processo che avviene in un'unica fase

L tiroxina liquida

Oral Liquid Formulation of Levothyroxine Is Stable in Breakfast Beverages and May Improve Thyroid Patient Compliance

Alberto Bernareggi , Elia Grata , Maria Teresa Pinorini and Ario Conti

Abstract: Patients on treatment with levothyroxine (T4) are informed to take this drug in the morning, at least 30 min before having breakfast. A significant decrease of T4 absorption was reported, in fact, when T4 solid formulations are taken with food or coffee. According to preliminary clinical study reports, administration of T4 oral solution appears to be less sensitive to the effect of breakfast beverages on oral bioavailability. In the present study, stability of T4 oral solution added to breakfast beverages was investigated. A 1 mL ampoule of single-dose Tirosint® oral solution (IBSA Farmaceutici Italia, Lodi, Italy) was poured into defined volumes of milk, tea, coffee, and coffee with milk warmed at 50 °C, as well as in orange juice at room temperature. Samples were sequentially collected up to 20 min and analyzed by validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. The results of the study demonstrated that T4 is stable in all beverages after 20 min incubation. Demonstration of T4 stability is a prerequisite for a thorough evaluation of the effect of breakfast beverages on the bioavailability of T4 given as oral solution and for a better understanding of the reasons underlying a decreased T4 bioavailability administered as solid formulations.

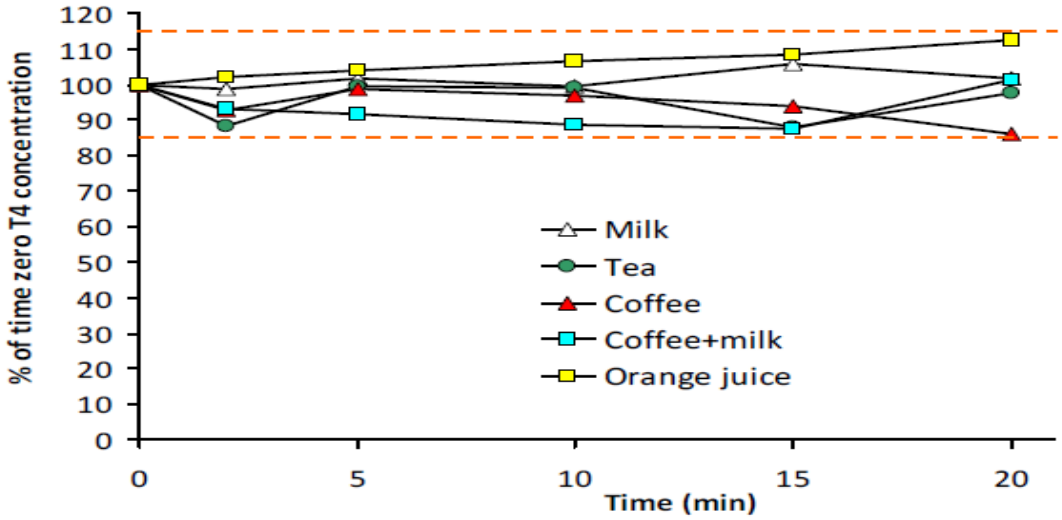
Pharmaceutics **2013**, *5*, 621-633

L tiroxina liquida

Oral Liquid Formulation of Levothyroxine Is Stable in Breakfast Beverages and May Improve Thyroid Patient Compliance

Alberto Bernareggi , Elia Grata , Maria Teresa Pinorini and Ario Conti

Graphical representation of mean percent variation of T4 concentration as a function of time with respect to time zero concentration for all tested beverages. Dashed lines indicate the acceptance limits of ±15% of time zero concentrations.



Pharmaceutics **2013**, *5*, 621-633

L tiroxina liquida

Clin. Pharmacokinet. 2004;43(14):1037-53.

Abstract

OBJECTIVES:

Assessment of relative bioavailability of levothyroxine sodium (L-T4) from eight solid preparations, compared with a liquid formulation, by using pharmacological doses, and critical evaluation of trial methodology based on the pooled analysis of individual data.

DESIGN:

Eight open-label, randomised, single-dose, crossover phase I studies using eight solid L-T4 dosage forms (25, 50, 75, 100, 125, 150, 175, 200 microg per tablet; administered total doses 600, 625 or 700 microg) and a liquid formulation; assessment of relative bioavailability by 90% confidence intervals for the relative area under the concentration-time curve (AUC) of total thyroxine (TT4), i.e. protein-bound plus free thyroxine, calculated by using the recommended log AUC four-way analysis of variance models for crossover designs. For the pooled analysis, general linear models were applied to assess the validity of model assumptions, to identify potential sources of effect modification, to discuss alternative modelling approaches with respect to endogenous hormone secretion and to give recommendations for future designs and sample sizes.

PARTICIPANTS:

One hundred and sixty-nine healthy males; 29 of these individuals participating in two studies.

INTERVENTIONS:

Single oral doses of L-T4 tablets and the liquid formulation administered after fasting, separated by at least 6 weeks; a total of 396 drug exposures.

MAIN OUTCOME MEASURES:

TT4 AUC from 0 to 48 hours and peak plasma concentration with and without baseline correction.

RESULTS:

Each study demonstrated equivalence of the tablets to the drinking solution, independent of the chosen analysis model. Sequence effects that could devalidate the chosen crossover approach were not found. Period effects with changing directions that could best be explained by seasonal variation were detected. While the pre-specified method of baseline correction of simply subtracting individual time-zero TT4 values was disadvantageous, the analysis of total AUC could be improved considerably by covariate adjustment for baseline TT4. With this approach, sample sizes could have been substantially reduced or, alternatively, the recommended equivalence ranges could be reduced to +/-6%.

CONCLUSION:

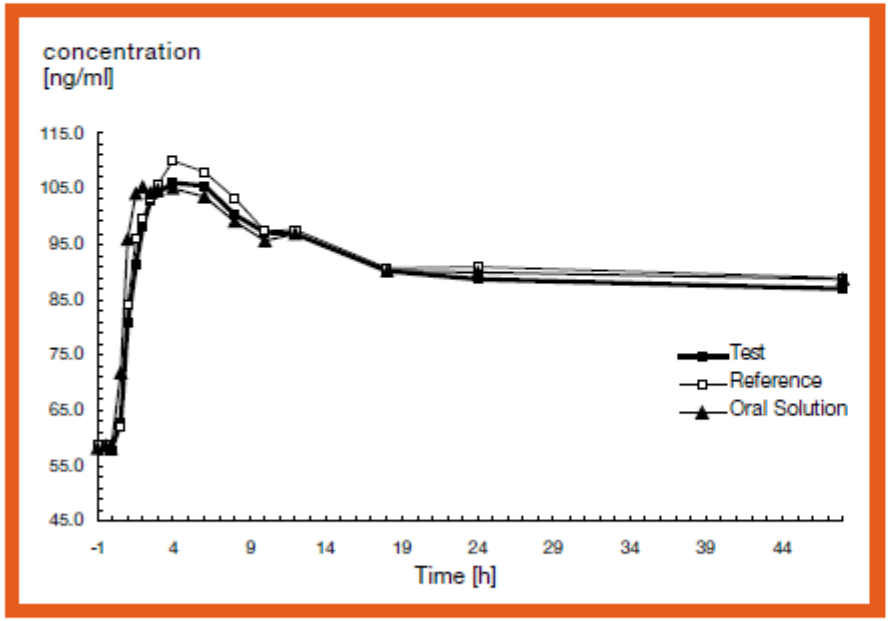
Using a single pharmacological dose of L-T4 in two-period crossover designs is a safe and reliable procedure to assess L-T4 dosage form performance. With an adequate statistical modelling approach, the design is efficient and allows general conclusions with moderate sample sizes

L tiroxina liquida

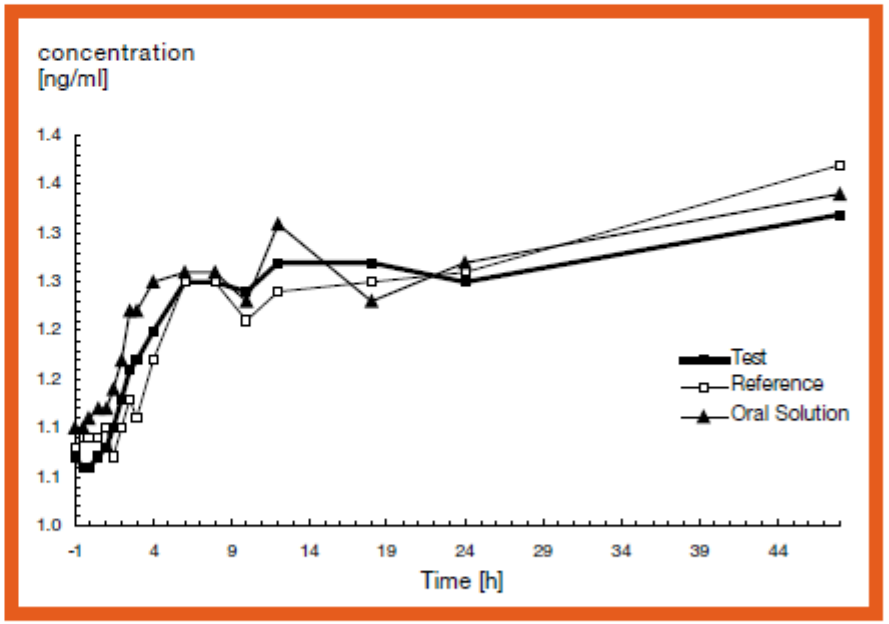
Bioequivalence Study of Levothyroxine Tablets Compared to Reference Tablets and an Oral Solution

Rossen Koytchev and Reinhard Lauschner

The study was designed to evaluate the bioequivalence of three levothyroxine sodium (CAS 51-48-9) formulations, i.e. a test and a reference tablet and an oral solution. A bioequivalence study was carried out in 25 healthy volunteers, who were administered a single dose of 600 µg levothyroxine in the form of the test formulation (levothyroxine sodium tablets 200 µg; Eferox®), the originator product, and an oral solution. The trial was performed in one study center according to an open, randomized, three-way cross-over design with wash-out periods of 35 days between administration.



Mean concentration-time curves of levothyroxine after administration of the test (■) and reference (□) tablets as well as oral solution (▲).



Mean concentration-time curves of triiodthyronine after administration of the test (■) and reference (□) tablets as well as oral solution (▲).

Arzneim.-Forsch./Drug Res. 54, No. 10, 680–684 (2004)

L tiroxina liquida

Congenital Hypothyroidism Treatment in Infants: A Comparative Study between Liquid and Tablet Formulations of Levothyroxine

Peroni E.* · Vigone M.C.* · Mora S.* · Bassi L.A.* · Pozzi C.* · Passoni A.* · Weber G.*

*Department of Pediatrics and *Laboratory of Pediatric Endocrinology, Division of Metabolic and Cardiovascular Sciences, San Raffaele Scientific Institute, Vita-Salute University, Milan, Italy
Horm Res Paediatr 2014;81:50-54

Abstract

Aims: To compare the effects of liquid and tablet formulations of levothyroxine (L-T4) in 78 newborns with congenital hypothyroidism (CH). *Methods:* 39 patients received liquid L-T4 (group A) and 39 patients received tablets (group B). Thyroid-stimulating hormone (TSH) and free thyroxine (fT4) were measured and L-T4 dose recorded at onset of therapy and during the first year of treatment. Developmental quotient (DQ) was assessed by Griffiths' mental development scales at 12 months of age. *Results:* Gestational age, birth weight, screening TSH, etiology and severity of CH, age at onset of therapy and median initial L-T4 dose were similar in both groups. fT4 concentration normalized before 10 days of treatment in all patients. Normalization of TSH concentration was achieved after 7-10 days of therapy in 87% of group A patients and in 82% of group B patients. Group A patients had significantly lower TSH values compared with those of group B at 7-10 days ($p = 0.05$) and 6-8 months ($p = 0.043$) of treatment, despite similar L-T4 dose and fT4 concentration. Mean DQ scores were within normal range in all patients. *Conclusion:* We confirmed the efficacy and safety of both formulations. The TSH inhibition trend when using liquid L-T4 may be linked to a higher absorption in comparison to the tablets

L tiroxina liquida

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

J. Pediatr. 2013; 162:1264-1269

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.

L tiroxina liquida

Oral Liquid L-Thyroxine (L-T4) May Be Better Absorbed Compared to L-T4 Tablets Following Bariatric Surgery

Ilenia Pirola · Anna M. Formenti · Elena Gandossi · Francesco Mittempergher · Claudio Casella · Barbara Agosti · Carlo Cappelli

OBES SURG (2013) 23:1493–1496

Abstract Drug malabsorption is a potential concern after bariatric surgery. We present four case reports of hypothyroid patients who were well replaced with thyroxine tablets to euthyroid thyrotropin (TSH) levels prior to Roux-en-Y gastric bypass surgery. These patients developed elevated TSH levels after the surgery, the TSH responded reversibly to switching from treatment with oral tablets to a liquid formulation.

Thyroid parameters measured at the indicated times in four patients who underwent bariatric surgery between 2009 and 2011. Patients were receiving oral L-T4 in either tablet or liquid form as indicated

	Before surgery L-T4 in tablet form				12 Months after surgery L-T4 in tablet form				14 Months after surgeryL-T4 in liquid form				17 Months after surgery L-T4 in tablet form			
Patient	L-T4 (μg)	TSH	fT4	fT3	L-T4 (μg)	TSH	fT4	fT3	L-T4 (μg)	TSH	fT4	fT3	L-T4 (μg)	TSH	fT4	fT3
1	200	4.2	12.7	3.1	200	18.1	10.4	2.9	200	1.5	12.9	3.8	200	36.7	9.8	3.0
2	150	3.1	12.9	3.3	150	12.1	10.2	3.2	150	1.9	13.5	4.0	150	24.7	10.4	3.2
3	200	3.9	11.7	3.7	200	20.4	10.2	3.3	200	0.6	13.5	3.2	200	17.7	10.2	3.1
4	150	3.6	10.9	3.2	150	17.2	11.0	2.8	150	2.4	11.9	3.2	150	15.3	10.1	3.1

L-T4 levothyroxine, *TSH* thyrotropin, *fT4* free tyroxine, *fT3* free triiodothyronin

L tiroxina liquida

Valentina ha un TSH di 210 µU/ml, continua a riferire astenia, sensazione di gonfiore, sonnolenza continua nell'arco della giornata

Viene sostituito Tirosint cp con Tirosint Soluzione Orale

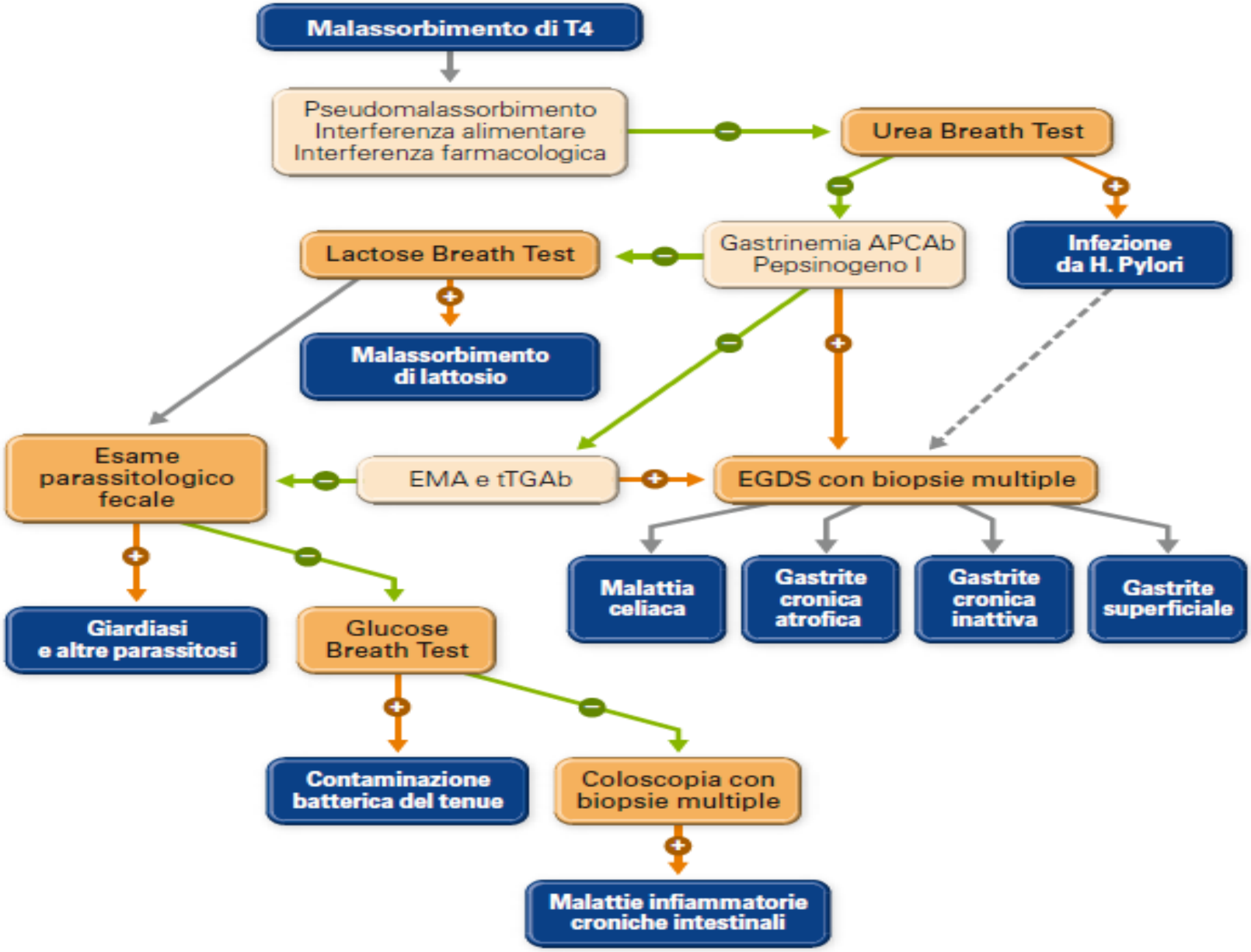
Viene aumentato ulteriormente il dosaggio fino a 200 mcrg/die)

Viene richiesto un controllo dopo 40 giorni, che in realtà viene effettuato diversi mesi più tardi (luglio 2011) con riscontro di TSH = 355 µU/ml

L tiroxina liquida

Si programma un ulteriore, progressivo incremento di dose fino a 300 mcgr/die

Si programma uno studio dei possibili fattori responsabili di tale resistenza alla terapia


Malassorbimento di T4
Pseudomalassorbimento
Interferenza alimentare
Interferenza farmacologica
Urea Breath Test
Lactose Breath Test
Gastrinemia APCAb
Pepsinogeno I
Infezione da H. Pylori
Malassorbimento di lattosio
Esame parassitologico fecale
EMA e tTGAb
EGDS con biopsie multiple
Giardiasi e altre parassitosi
Glucose Breath Test
Malattia celiaca
Gastrite cronica atrofica
Gastrite cronica inattiva
Gastrite superficiale
Contaminazione batterica del tenue
Coloscopia con biopsie multiple
Malattie infiammatorie croniche intestinali

RISULTATI:

ESAMI EMATICI: tutti nella norma
BREATH TEST: negativi
ESAMI PARASSITOLOGICI: negativi
EGDS: negativa

DIAGNOSI

IPOTIROIDISMO REFRATTARIO PER MALASSORBIMENTO SELETTIVO DI TIROXINA ORALE

L tiroxina iniettiva

Parenteral Thyroxine Administration

Marguerite T. Hays, M.D.

THYROID
Volume 17, Number 2, 2007

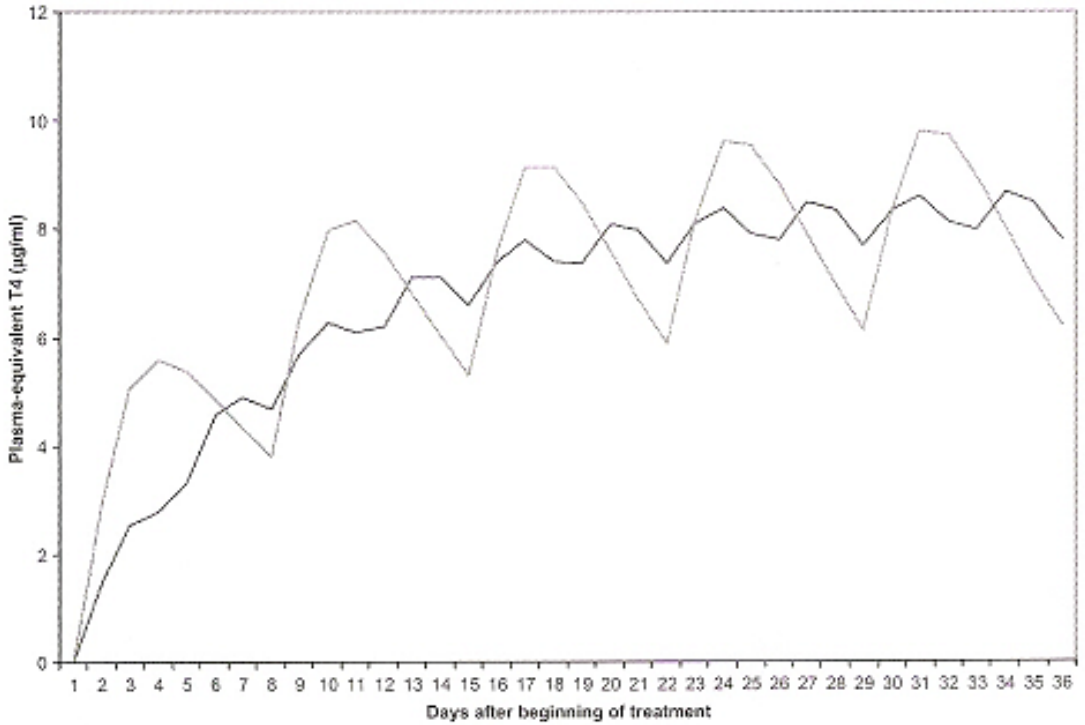
Parenteral Administration of T4

There are no guidelines for parenteral administration, and the patients reported have been treated empirically. Intravenous (iv) T4 has been given, generally daily or 3–5 times weekly. One patient is reported to have responded well to both intramuscular (im) and subcutaneous (sc) T4, but sc administration caused pain at the injection site

The commercially available injectable T4 is labeled for either iv or im, but not sc, injection Perhaps the formulation could be modified to permit sc administration.

A tracer study of the kinetics of labeled T4-injected sc compared with iv administration showed the sc tracer to be well absorbed and to enter the circulation gradually, leaving the injection site with a mean half life of 20 hours. Pilot studies with im administration showed somewhat faster T4 release into the circulation than with sc injection

L tiroxina iniettiva



Model projections of thyroxine (T4) concentration in the slow-exchange compartment after intramuscular administration of 750 µg T4 weekly (coarser fluctuations) or 375 µg T4 twice weekly (finer fluctuations). The model assumes the T4 exchange parameters reported by Hays and McGuire (10) and an initial zero concentration of T4.

Parenteral Thyroxine Administration

Marguerite T. Hays, M.D.

THYROID
Volume 17, Number 2, 2007

L tiroxina iniettiva

A Settembre 2013 Valentina inizia terapia con tiroxina parenterale (i.m. alla dose di 500 mcrg/settimana)

500/7 gg

L-Thyroxin Henning inject

514 Mikrogramm, Pulver und Lösungsmittel zur Herstellung einer Injektions- oder Infusionslösung

1 Durchstechflasche mit 55 mg Pulver und **1** Ampulle mit Lösungsmittel zur Herstellung einer Injektions- oder Infusionslösung

ASP - AZIENDA SANITARIA LOCALE POTENZA
POLIAMBULATORIO "MADRE TERESA"
(RESP.DR.V.BARILE)
DIPARTIMENTO MEDICINA DI LABORATORIO
(RESP.DR.D.CAVALIERE)
VIA DEL GALLITELLO - POTENZA
TEL. 0971-310839

Pratica numero: 30112
Prelievo del: 19/11/2013
Data del Referto: 21/11/2013
Ente: ENDOCRINOLOGIA

[redacted] VALENTINA
Data di Nascita: 25/04/1989
Sesso: Femminile
[redacted]

Esame Richiesto	Risultati		Valori di Riferimento Donne
FT3	2.39	pg/ml	<*> 1.71 - 3.71
FT4	1.08	ng/dl	<*> 0.70 - 1.48
TSH	25.39	uIU/ml	< >* 0.35 - 4.94

500/5 gg

L-Thyroxin Henning® inject

514 Mikrogramm, Pulver und Lösungsmittel zur Herstellung einer Injektions- oder Infusionslösung

Levothyroxin-Natrium

Schilddrüsentherapeutikum

Intravenöse Anwendung nach Zubereitung

1 Durchstechflasche mit 55 mg Pulver und
1 Ampulle mit Lösungsmittel zur Herstellung einer Injektions- oder Infusionslösung

SANOFI

ASP - AZIENDA SANITARIA LOCALE POTENZA
POLIAMBULATORIO "MADRE TERESA"
(RESP.DR.V.BARILE)
DIPARTIMENTO MEDICINA DI LABORATORIO
(RESP.DR.D.CAVALIERE)
VIA DEL GALLITELLO - POTENZA
TEL. 0971-310839

Pratica numero: 32931
Prelievo del: 07/01/2014
Data del Referto: 07/01/2014
Ente: ENDOCRINOLOGIA

[redacted] VALENTINA
Data di Nascita: 25/04/1989
Sesso: Femminile
[redacted]

Esame Richiesto	Risultati		Valori di Riferimento Donne
FT3	2.94	pg/ml	<*> 1.71 - 3.71
FT4	1.30	ng/dl	<*> 0.70 - 1.48
TSH	13.09	uIU/ml	< >* 0.35 - 4.94

500/4 gg

ASP - AZIENDA SANITARIA LOCALE POTENZA
POLIAMBULATORIO "MADRE TERESA"
(RESP.DR.V.BARILE)
DIPARTIMENTO MEDICINA DI LABORATORIO
(RESP.DR.D.CAVALIERE)
VIA DEL GALLITELLO - POTENZA
TEL. 0971-310839

Pratica numero: 38281
Prelievo del: 12/03/2014
Data del Referto: 18/03/2014
Ente: POTENZA GALLITELLO

[redacted] VALENTINA
Data di Nascita: 25/04/1989
Sesso: Femminile
[redacted]

Esame Richiesto	Risultati		Valori di Riferimento Donne
FT3	3.27	pg/ml	<*> 1.71 - 3.71
FT4	1.27	ng/dl	<*> 0.70 - 1.48
TSH	2.14	uIU/ml	<*> 0.35 - 4.94

L tiroxina generica

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Volume 98 Issue 2 | February 1, 2013.

Generic vs Name Brand L-Thyroxine Products: Interchangeable or Still Not?
James V. Hennessey
98 (2) pp 511 – 514

Generic and Brand-Name l-Thyroxine Are Not Bioequivalent for Children With Severe Congenital Hypothyroidism
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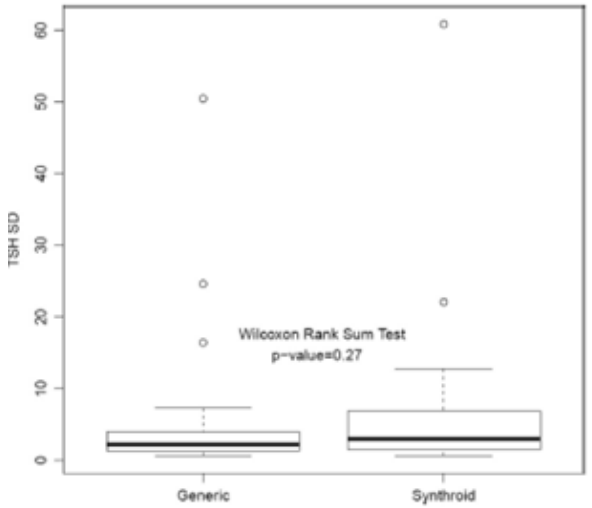

Median (upper, lower quartile range) TSH SD in children treated with Synthroid and generic LT4 using Wilcoxon rank sum test.

Our study has several limitations. First, it was retrospective, and drug choice was not randomly assigned.

the patient was taking generic LT4 or Synthroid was determined by prescription records in their chart, which may not reflect what they actually received from the pharmacy.

Additionally, due to the retrospective nature of the study, there is no way to verify a standard method of administering the LT4 pills, such as taking at the same time of day or on an empty stomach.

compliance with treatment could not be verified

TSH and free T_4 assays were not always done at our center, and this may have contributed some to the variability observed

L tiroxina generica

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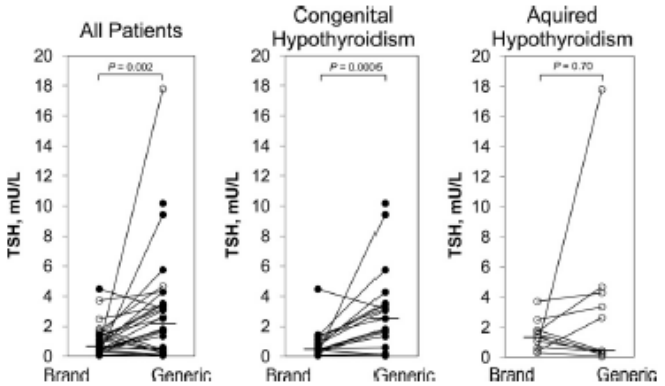

Serum TSH concentration after 8 weeks of brand-name L-T_4 vs generic formulation. Closed circles denote patients with congenital hypothyroidism; open circles indicate patients with acquired hypothyroidism. Lines connect paired data. The horizontal bar indicates the median value. The serum TSH concentration was significantly greater after generic vs brand-name product, but subgroup analysis revealed that this difference was seen only in patients with CH.

Design: This was a prospective randomized crossover study in which patients received 8 weeks of one L-T_4 formulation followed by 8 weeks of the other.

Conclusions: Synthroid and an AB-rated generic L-T_4 are not bioequivalent for patients with severe hypothyroidism due to CH, probably because of diminished thyroid reserve. It would therefore seem prudent not to substitute L-T_4 formulations in patients with severe CH, particularly in those <3 yr of age. Our results may have important implications for other severely hypothyroid patients in whom precise titration of L-T_4 is necessary.

L tiroxina generica

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Until better data become available, I will continue to follow the AACE/ATA/TES recommendations on LT4 treatment in my practice. Physicians should: 1) alert patients that preparations may be switched at the pharmacy; 2) encourage patients to ask to remain on the same preparation at every pharmacy refill; and 3) make sure patients understand the need to have their TSH retested and the potential for dosing readjusted every time their LT4 preparation is switched

L tiroxina generica

Comunicazione AIFA sui medicinali contenenti levotiroxina sodica (15-11-2013)

Con riferimento all'inserimento nella lista di trasparenza di specialità medicinali contenenti levotiroxina sodica si fa presente quanto segue:

"Nella maggior parte dei casi trattati un prodotto a base di levotiroxina è automaticamente sostituibile con un analogo generico, con la sola precauzione di un controllo dei valori di TSH e FT4 dopo quattro-sei settimane, e con particolare cautela nelle circostanze in cui è richiesta maggiore attenzione nel mantenere l'equilibrio tiroideo, ovvero:

- donne in gravidanza o che stiano pianificando il concepimento;
- ipotiroidismo, congenito o acquisito, in età pediatrica;
- terapia soppressiva in pazienti con pregresso carcinoma tiroideo, soprattutto se fragili o anziani;
- pazienti con ipotiroidismo centrale.

In questi pazienti l'eventuale passaggio ad una diversa formulazione richiede l'informazione del paziente e dovrebbe essere seguito dal controllo del TSH sierico (e della FT4 nell'ipotiroidismo centrale) dopo quattro-sei settimane di terapia".

Fonte: www.agenziafarmaco.gov.it

Dep. presso AIFA il 25/11/2013

L tiroxina generica

Documento redatto a cura delle Società Scientifiche

Tuttavia, i prodotti a base di levotiroxina vengono considerati simili senza il supporto di dati clinici e di bioequivalenza, come previsto dagli standard raccomandati dalle principali Società Scientifiche. Ad oggi, infatti, le principali Società Scientifiche internazionali ritengono necessari ulteriori studi per valutare opportunamente la farmacocinetica dei prodotti a base di levotiroxina e la capacità di quest'ultima di predire l'esito clinico. Negli Stati Uniti, tutte le società scientifiche di riferimento per le malattie della tiroide (American Association of Clinical Endocrinology - AACE, l'American Thyroid Association - ATA, e The Endocrine Society - TES) hanno emanato un documento comune (http://www.thyroid.org/thyroxine-products-joint-position-statement/) sull'intercambiabilità dei prodotti a base di levotiroxina in cui dispongono le seguenti raccomandazioni:

Per il Medico Curante: I pazienti in corso di terapia con levotiroxina sodica devono essere mantenuti in trattamento con lo stesso prodotto. Se la preparazione viene cambiata, si rende necessario un controllo preciso ed accurato del TSH nei pazienti con ipotiroidismo primario e delle FT4 nei pazienti con ipotiroidismo centrale, entro 6 settimane per evitare potenziali effetti iatrogeni indesiderati.

Per il Paziente: Le malattie della tiroide spesso richiedono un trattamento con levotiroxina sodica per lunghi periodi di tempo. E' importante che il trattamento sia costante e preciso, e che sia utilizzata la stessa preparazione di levotiroxina sodica anche quando il Medico Curante ne modifichi il dosaggio. Quindi, quando si reca in farmacia, non accetti la sostituzione della preparazione a base di levotiroxina sodica senza l'approvazione del Medico Curante.

L tiroxina generica

Documento redatto a cura delle Società Scientifiche

In conclusione, fino a quando non saranno resi disponibili standard di qualità più rigorosi e l'introduzione di nuovi ed affidabili test che valuteranno l'intercambiabilità dei prodotti a base di levotiroxina, è opportuno, nel migliore interesse del paziente, continuare a ritenerli prodotti unici non sostituibili, come raccomandano le principali Società Scientifiche internazionali e molte Agenzie Regolatorie di diversi Paesi.

18 novembre 2013

L tiroxina soft gel

www.associazionemediciendocrinologi.it
Breaking news
nr. 12 - marzo 2014

Dosaggio	Colore del confezionamento	Classe	Prezzo
Tiche 13 microgrammi		C	7,55 €
Tiche 25 microgrammi		C	7,55 €
Tiche 50 microgrammi		C	7,55 €
Tiche 75 microgrammi		C	7,55 €
Tiche 88 microgrammi		C	7,85 €
Tiche 100 microgrammi		C	7,85 €
Tiche 112 microg		C	7,85 €
Tiche 125		C	7,85 €
Tiche 137 m		C	8,25 €
Tiche 150 mic		C	8,25 €
Tiche 175 microgrammi		C	8,25 €
Tiche 200 microgrammi		C	8,25 €

involucro in gelatina che contiene all'interno tiroxina veicolata in un liquido idrofilico viscoso; esse **presentano il vantaggio di tempi di dissoluzione e di assorbimento più rapidi rispetto alle compresse.**

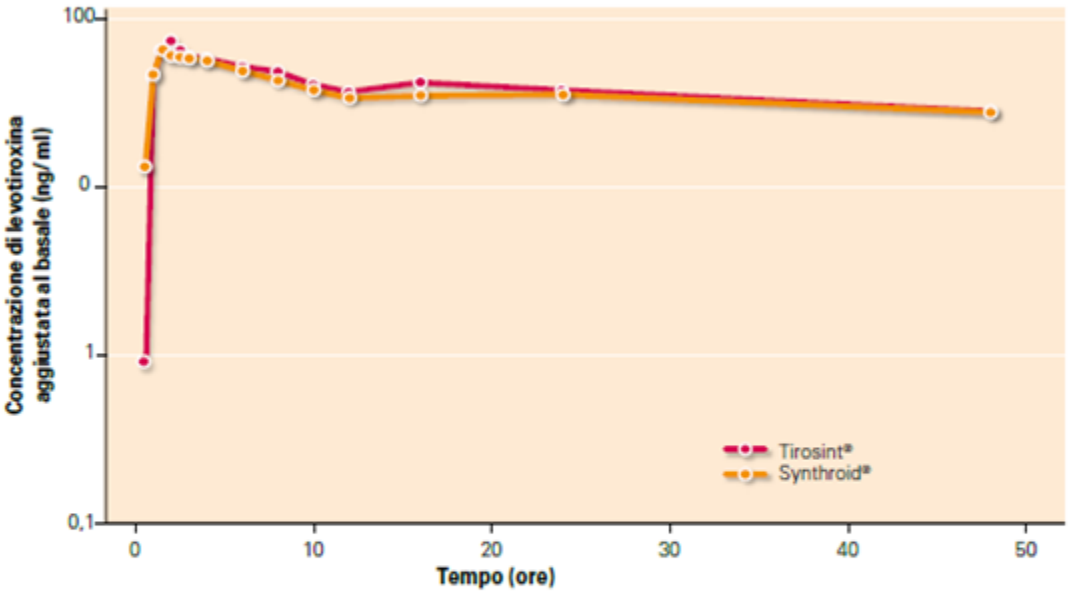
L tiroxina soft gel

Assessment of levothyroxine sodium bioavailability

Clin. Pharmacokinet. 2004; 43: 1037-1053

Disegno dello studio di comparazione farmacocinetica fra capsule molli e compresse di levotiroxina.		
	Studio di equivalenza farmacocinetica che confronta le capsule molli Tirosint® con la compresse Synthroid®	
Disegno dello studio	Studio di equivalenza farmacocinetica randomizzato, cross-over in dose singola, a due vie, due periodi	
Soggetti	Soggetti sani dai 18 ai 50 anni di età: 14 maschi + 14 femmine	
Demografia	Età:	32 ± 7 anni
	Peso:	67,7 ± 10,4 kg
	Etnia:	Caucasici (54%) Ispanici (43%) Afroamericani (3%)
Dose	4 × 150 µg	
Washout	35 giorni	
Campionamento	Tre campionamenti predose; campionamenti sequenziali fino a 48 ore postdose	
Sicurezza	Segni vitali; monitoraggio del TSH; monitoraggio continuo di eventi avversi	

Capsule molli Tirosint® vs compresse Synthroid®



Parametro	Media geometrica		Ratio (test/ref)	Intervallo di confidenza al 90%
	Tirosint®	Synthroid®		
AUC_{0-48} (ng·h/ml)	1703	1654	103,0%	92,8 - 114,4%
C_{max} (ng/ml)	75,54	70,74	106,8%	100,7 - 113,2%
T_{max} (h)*	2,9	2,1	–	–

* Media aritmetica per T_{max}.

AUC_{0-48}, area sotto la curva tempo-concentrazione da 0 a 48 ore; C_{max}, concentrazione massima; T_{max}, tempo per arrivare alla C_{max}.

L tiroxina soft gel

TABLET LEVOTHYROXINE (L-T4) MALABSORPTION INDUCED BY PROTON PUMP INHIBITOR: A PROBLEM THAT WAS SOLVED BY SWITCHING TO L-T4 IN SOFT GEL CAPSULE.

Roberto Vita, MD ; Salvatore Benvenga, MD

***ENDOCRINE PRACTICE* Rapid Electronic Article**

L-T4 dose (µg/day)	TSH (mU/L)			Pantoprazole (40 mg/day)
	Tablet	Soft gel capsule	Tablet	
100	4.4-6.5	2.4	3.2-4.7	Yes
125	2.4	0.5	2.7-3.0	Yes
150	0.6	-	-	Yes

L tiroxina soft gel

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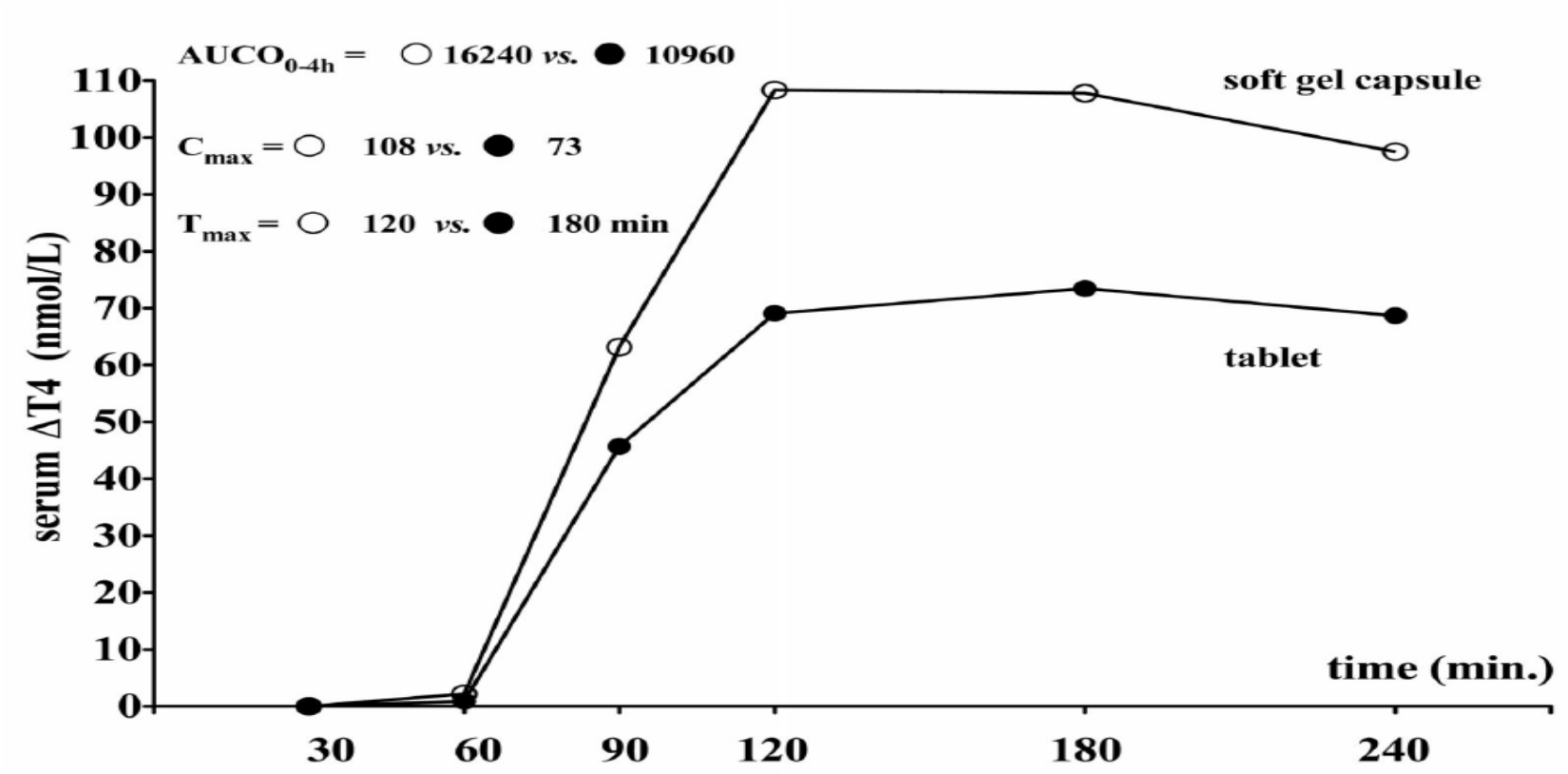
ENDOCRINE PRACTICE **Rapid Electronic Article**



L tiroxina soft gel

A novel formulation of l-thyroxine (l-T4) reduces the problem of l-T4 malabsorption by coffee observed with traditional tablet formulations

- Roberto Vita, Giovanna Saraceno, Francesco Trimarchi, Salvatore Benvenga

Endocrine 2013; 43: 154-160

Abstract

The purpose of this work is to evaluate if the coffee-associated malabsorption of tablet levothyroxine (l-T4) is reduced by soft gel capsule. We recruited 8 patients with coffee-associated l-T4 malabsorption including one hypothyroid patient. For 6 months, the patients were switched to the capsule maintaining the l-T4 daily dose. Patients took the capsule with water, having coffee 1 h later (proper habit, PH) on days 1–90, or with coffee =5 min later (improper habit, IH) on days 91–180. After 6 months, 2 patients volunteered for an acute loading test of 600 μg l-T4 (capsule) ingested with water (PH) or with coffee (IH). In the single hypothyroid patient, the post-switch TSH ranged 0.06–0.16 mU/L (PH) versus 5.8–22.4 mU/L pre-switch (PH) and 0.025–0.29 mU/L (IH) versus 26–34 mU/L pre-switch (IH). In the other 7 patients, post-switch TSH was 0.41 ± 0.46 (PH) versus 0.28 ± 0.20 pre-switch (PH) ($P = 0.61$) and 0.34 ± 0.30 (IH) versus 1.23 ± 1.47 pre-switch (IH) ($P < 0.001$). Importantly, TSH levels in PH versus IH habit did not differ post-switch ($P = 0.90$), but they did pre-switch ($P < 0.0001$). The proportions of post-switch TSH levels <0.10 mU/L with PH (33.3 %) or with IH (33.3 %) were borderline significantly greater than the corresponding pre-switch levels with PH (10.3 %) ($P = 0.088$) or with IH (0 %) ($P = 0.0096$). In the two volunteers, the l-T4 loading test showed that coffee influenced l-T4 pharmacokinetics minimally. **Soft gel capsules can be used in patients who are unable/unwilling to change their IH of taking l-T4.**

CONCLUSIONI

- **L'efficacia terapeutica delle cp di l tiroxina può essere inficiata da numerosi fattori legati soprattutto all'assorbimento intestinale**
- **Le nuove formulazioni di tiroxina possono avere un importante impatto pratico, rappresentando la soluzione ad alcuni frequenti problemi osservati nella pratica clinica**
- **Non vi sono al momento evidenze sicure circa la possibilità di switchare automaticamente tutti i pazienti dal brand al generico**
- **Le soluzioni orali, per i vantaggi di assorbimento e di biodisponibilità possono essere particolarmente adatte nella popolazione pediatrica e geriatrica**
- **Le nuove formulazioni potrebbero non essere convenienti dal punto di vista economico**

Salvatore Benvenga
(Messina)

Nella nostra personale casistica su più di 200 pazienti osservati in ambulatorio in un periodo di 12 mesi, in 13 casi si è osservato un malassorbimento di levotiroxina collegato all'assunzione di caffè o altri farmaci (fra cui in particolare PPI, carbonato di calcio e preparati di ferro, a volte in combinazione). Tornando alla questione dei costi sanitari e tenuto conto che questi 13 pazienti avevano effettuato – prima di giungere alla nostra osservazione – una media di 18 dosaggi ormonali (uno o più fra TSH, FT4 ed FT3) senza che il problema del malassorbimento di levotiroxina fosse stato risolto, è possibile quantificare in circa 300 euro per paziente il costo di questi dosaggi ormonali.

Calcolando la grande diffusione del trattamento con ormoni tiroidei e con PPI nella popolazione generale (2-10% e 10-20%, rispettivamente), si potrebbe arrivare a dover moltiplicare questi costi anche per un milione di persone nella sola Italia (su una popolazione di 60 milioni di persone).