Levothyroxine as an example of Narrow Therapeutic Index (NTI) drug : from physiology to regulatory requirements

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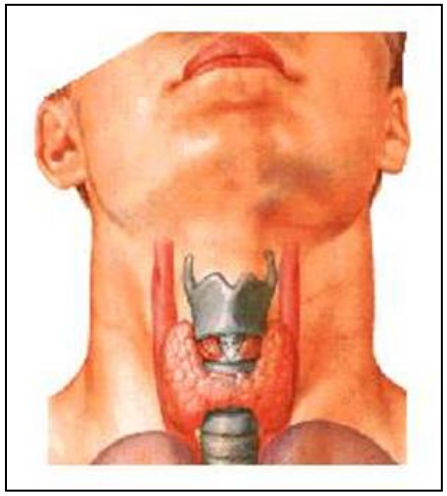
To be discussed

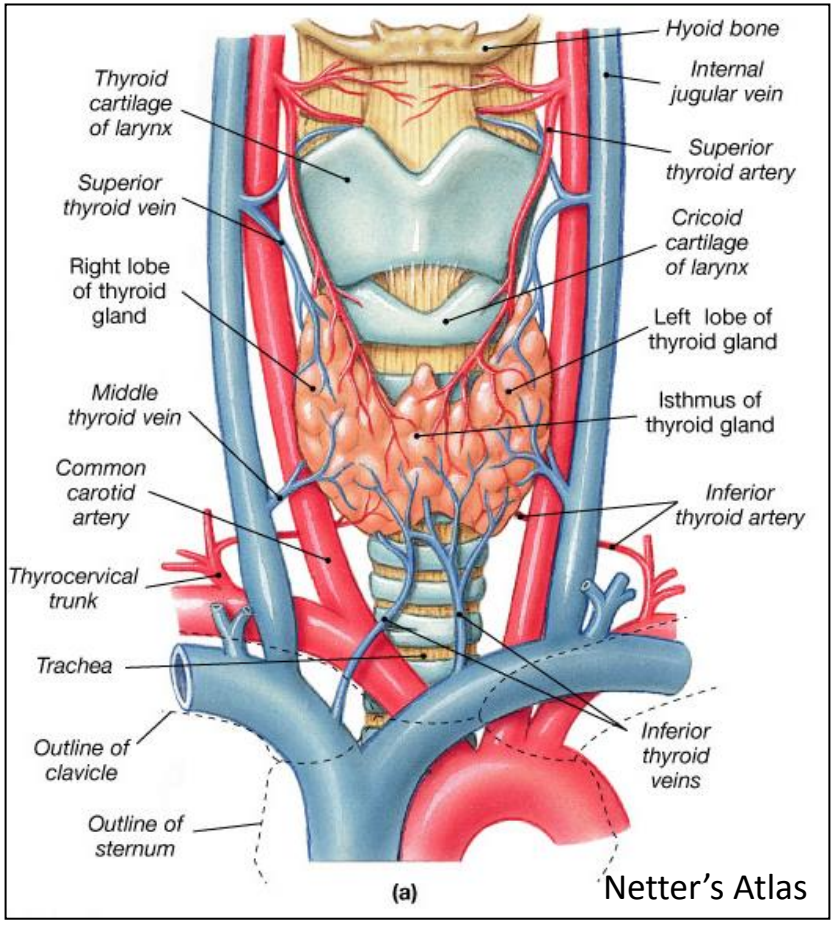
- 1) Brief review of thyroid function physiology

- 2) Past and new regulatory requirements for generic drugs of Levothyroxine

The Thyroid Gland



- Normally extends from Cervical C5 to Thoracic T1 vertebrae
- Butterfly shaped
- Two lateral lobes connected by an isthmus crossing the tracheal rings
- Pyramidal lobe not always present
- Attached to cricoid cartilage by ligaments
- Largest endocrine gland : 15 to 20 g ;
4 (L) x 2 (l) cm ; 20 – 40 mm thickness ; normally not palpable
- Usually four parathyroid glands closely related



Highly vascular gland :

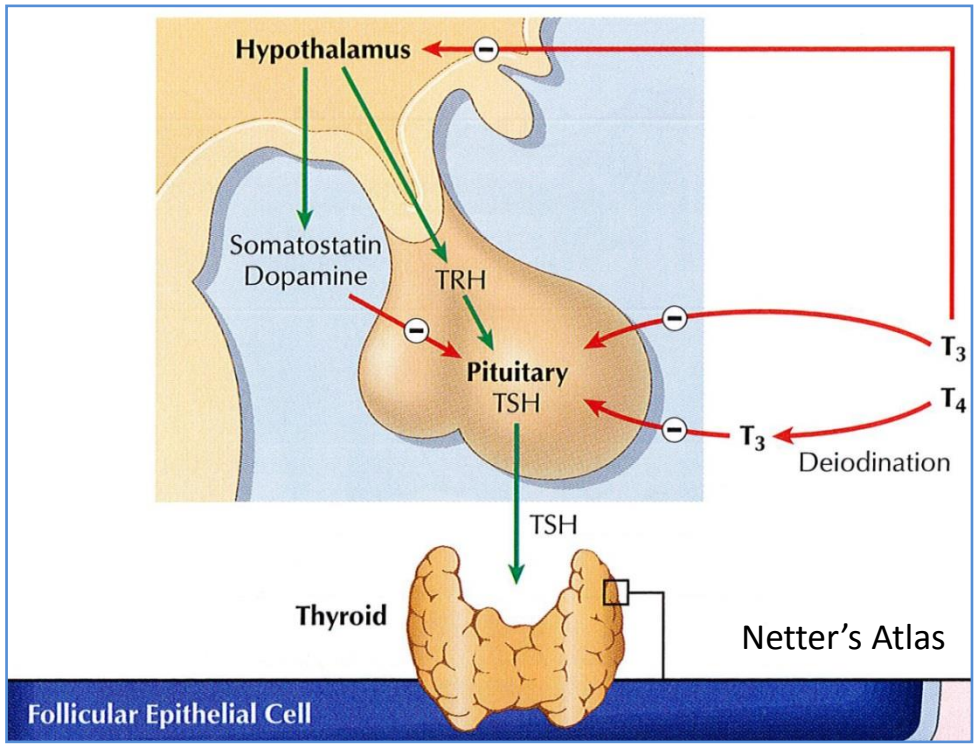
- Right/Left inferior and superior thyroid arteries
- Right/Left superior, middle and inferior thyroid veins
- Lymph vessels

Thyroid gland and thyroid hormone biosynthesis

- Iodide levels : negative feedback autoregulation
  - The rate of iodine uptake and incorporation into thyroglobulin (Tg) is influenced by the amount of iodide available : low iodide levels increase iodine transport into follicular cells ; high iodide levels decrease iodine transport into follicular cells.

- Thyroid Stimulating Hormone, TSH : positive regulation of thyroid follicular cells
  - TSH binds to specific cell surface receptors
  - TSH increases metabolic activity that is required to synthesize Tg and generate peroxide
  - TSH stimulates both iodine uptake and iodination of tyrosine resides on Tg.

Classical view of the regulation of the Hypothalamic-Pituitary-Thyroid axis

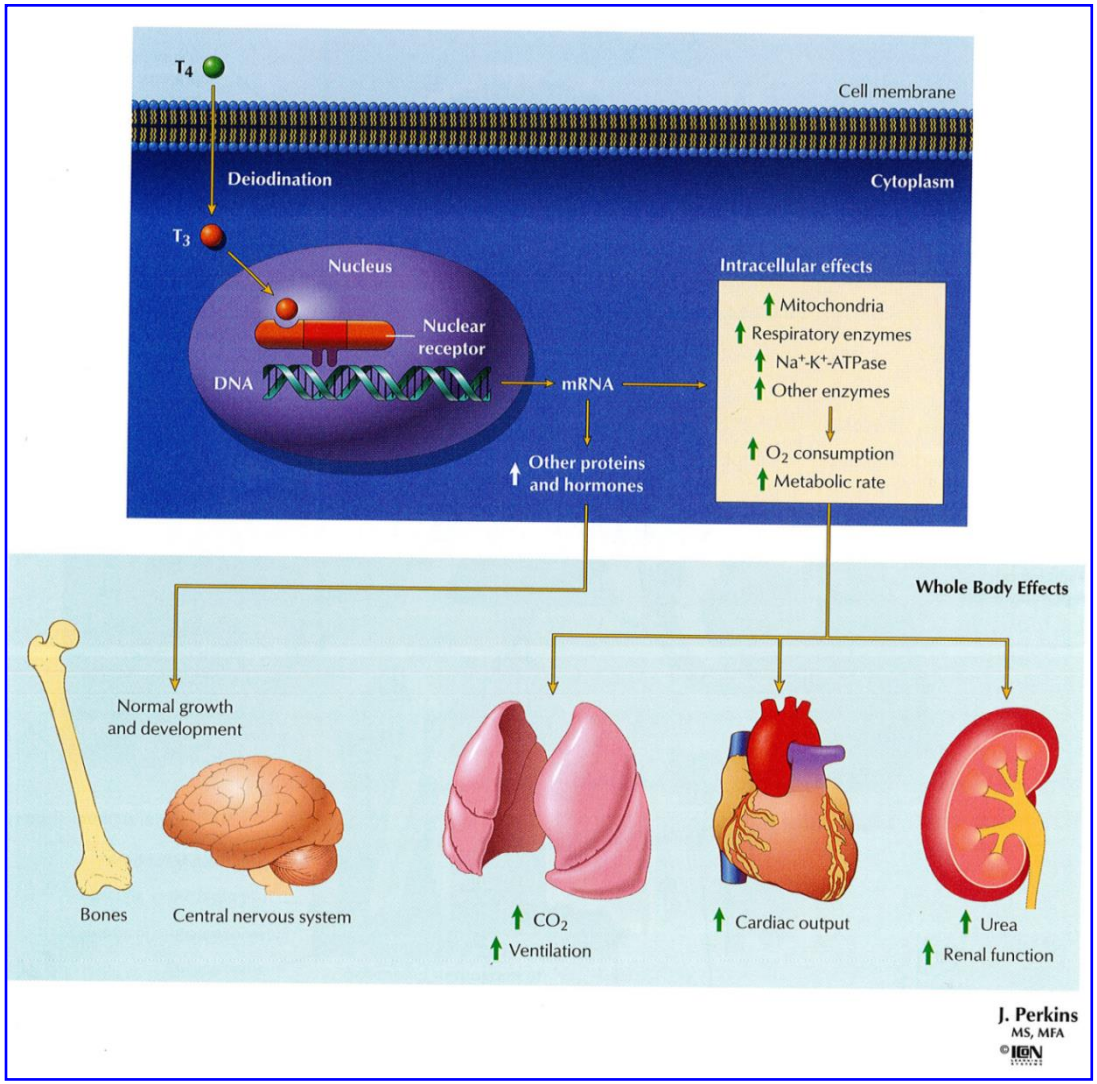


Thyrotropin-Releasing Hormone, **TRH** : tripeptide amide (pGlu-His-ProNH2) mainly secreted by a group of hypothalamic neurons of the paraventricular nucleus (lining the upper third of the third ventricle). TRH is critical for the synthesis and secretion of TSH.

TSH : anterior pituitary heterodimer glycoprotein (alpha subunit common to LH, FSH and hCG ; specific beta subunit)
Production rate : 50 to 200 mU/day with pulsatile secretion (peak at sleep onset and circadian variation).

- T_3 : approximately 50% of the feedback suppression of TSH release in the euthyroid state is attributed to plasma T_3 ; the other 50% requires local T_4 to T_3 conversion
- T_4 : suppression of TSH is independent of circulating T_4

Actions of Thyroid Hormones



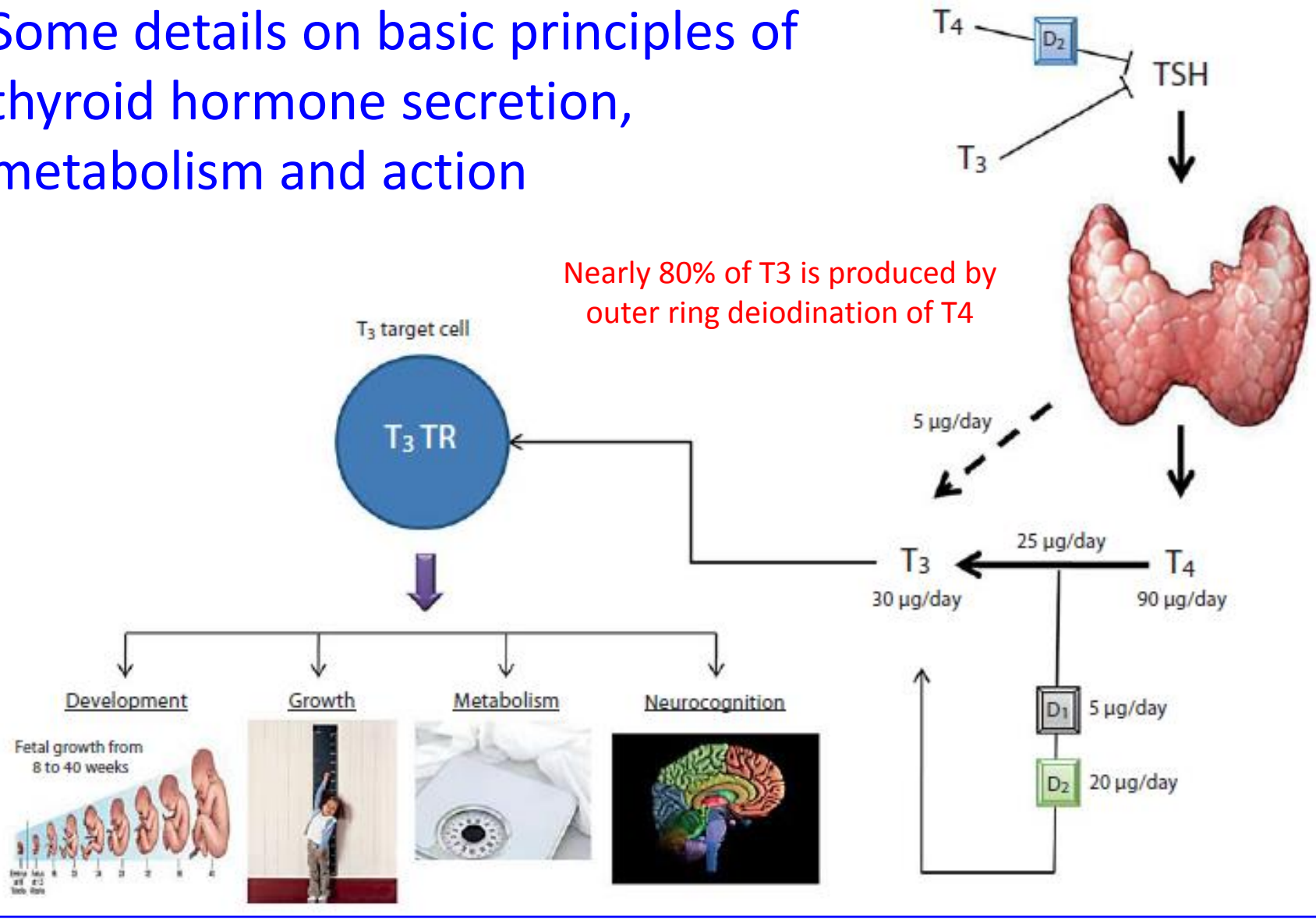
- Despite lipophilic nature of T_4 and T_3, two main active transporters are known :
  - OATP : organic anion-transporting polypeptide (OATP1C1 in brain blood vessels)
  - MCT : monocarboxylate transporter (MCT8 in tanycytes)

- T_4 deiodination to T_3 (see later)
- T_3 positively regulates the TRH gene via Thyroid Receptor $\alpha 1$
- T_3 negatively regulates the TRH gene via Thyroid Receptor ß

- T_3 negatively regulates the TSH ß gene via mainly TR $ß_2$
- T_3 decreases pituitary receptors for TRH
- T_3 can cause a rapid suppression of TSH release (mechanism ?)

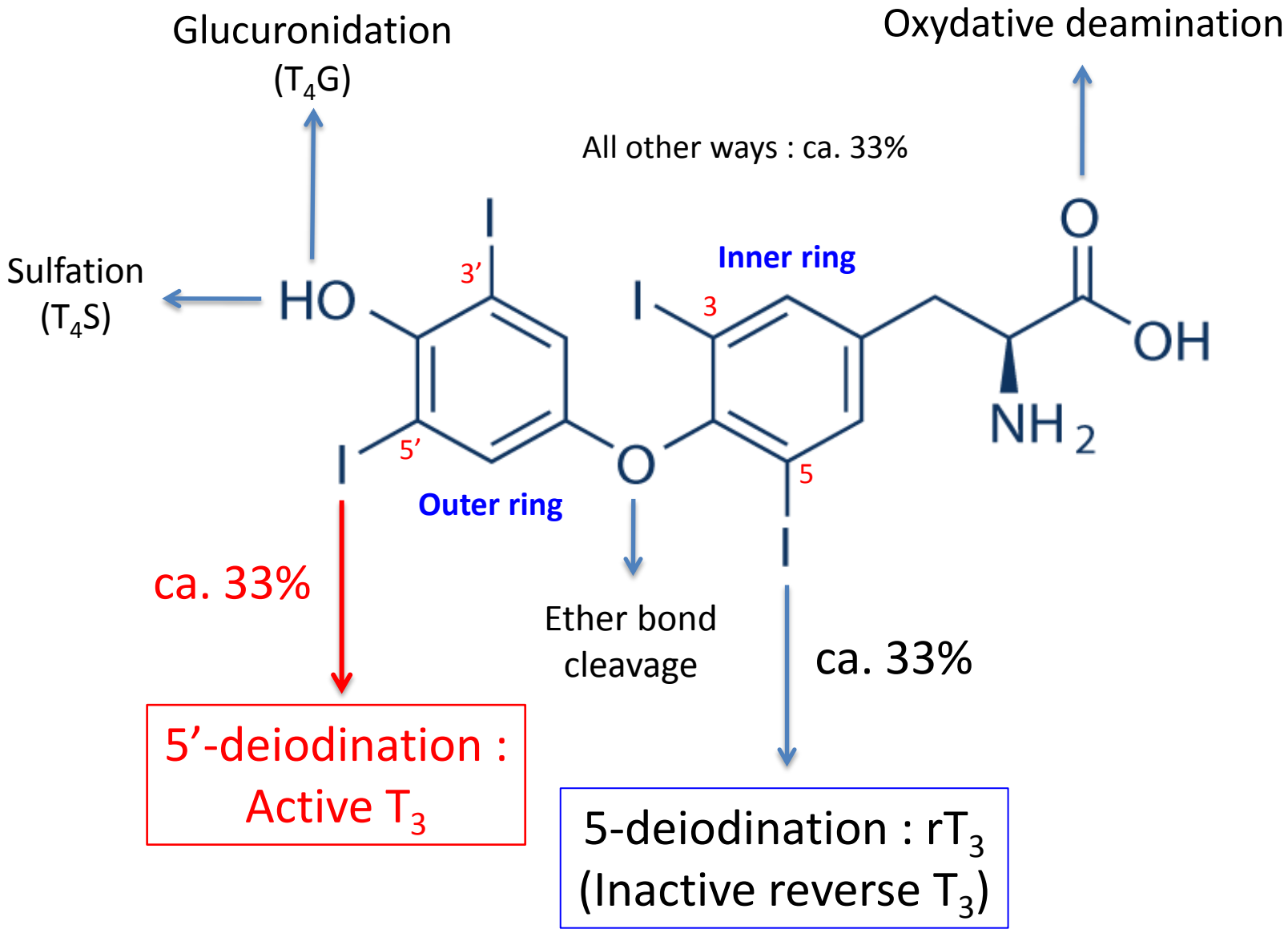
Thyroid hormones are vital to nervous system development, linear growth, energetic metabolism and thermogenesis, liver function, fluid balance and cardiovascular system

Some details on basic principles of thyroid hormone secretion, metabolism and action



In : Bianco and Casula, Eur Thyroid J, 2012;1/88-98

Pathways of Thyroxine (T_4) metabolism



Selenocysteine-containing iodothyronine deiodinases

	Type 1 Deiodinase D1	Type 2 Deiodinase D2	Type 3 Deiodinase D3
Location	Liver, Kidney, Thyroid	Brain, Pituitary, Muscles, BAT (animal)	Brain, Placenta, Fetal tissues (possible reexpression in pathophysiological conditions)
Deiodination	Inner/outer ring	Outer ring	Inner ring
Substrates	Inner : T_4 ➔ rT_3 Outer : T_4S ➔ T_3S	T_4 ➔ T_3	T_3 ➔ T_2 T_4 ➔ rT_3
Km values	T_4S : 0.3 µM T_4 : 2.3 µM	T_4 : 1 nM	T_3 : 10 nM T_4 : 37 nM
Main function	T_4 clearance ; recovery of iodide	Local T_3 production	T_3 degradation
Hypothyroidism	Decrease activity	Increase activity	Decrease activity
Hyperthyroidism	Increase activity	Decrease activity	Increase activity

Some key points

- Tanycytes (specialized glial celles) are one of the major sources of D2 mRNA
- In most brain regions, the primary role of D2 is to maintain local T_3 whenever circulating T_4 and T_3 decline
- [In hypothyroid rat, restoration of circulating levels of T_3 to normal levels without the administration of T_4 does not normalize TRH gene expression in the paraventricular nucleus ➔ critical role of D2 to produce T_3 from T_4]
- Local T_3 in the cortex is unchanged even if circulating T_4 vary over a relatively wide range
- Thyroid hormone signaling in individual tissues can change even though serum hormone concentrations are unaffected.

Typical reference ranges of blood thyroid tests

- TSH : 0.4-0.5 to 4.0-5.0 mU/L
  - Pulse every 2 hours ; maximal serum TSH reached between 21h and 2h ; difference between peak (night)and nadir (afternoon) is 1 to 3 mU/mL
- FT_4 : 12 – 22 pmol/L or 9.3 – 17. 1 ng/L
- Total T_4 : 45 – 120 ng/mL or 58 – 155 nmol/L
- FT_3 : 3.10 – 6.8 pmol/L or 2.0 – 4.4 ng/L
- Total T_3 : 0.8 – 2.0 ng/mL or 1.2 – 3.0 nmol/L

- Molecular weight : T4 = 777 Da ; T3 = 651 Da
- Daily production : T4 = 90 µg or 0.115 µM ; T3 = 35 µg or 0.054 µM

Pharmacokinetics of oral Levothyroxine

Parameter	Description
Main sites of absorption	Jejunum and ileum
Bioavailability	70 – 80% ; 15% decrease by concomitant food ; Decrease absorption if impaired gastric secretion (higher pH) ; Drug-drug interaction with PPIs (ex : omeprazole)
t_{max}	2 – 3 hours ; Food delays t_{max}
Protein binding	T4 : > 99.9% ; T3 : 99.8% (mainly Thyroxine-binding globulin ; albumin ; transthyretin). Restrictive binding
Volume of distribution	11 – 15 L ; Almost equivalent to extracellular fluid volume
Apparent elimination $t_{1/2}$	T4 : 7 days ; T3 : 1 day ; steady-state reached 4-6 weeks after initial therapy or changing Levothyroxine dosing
Typical oral dose, once daily	Adult over 50 y : 1.7 µg/kg/day (100 – 125 µg/day), 30 to 60 min before breakfast
Dose in bioequivalence study	Typically 600 µg ; a single large dose up to 3 mg in healthy subject was reported to be safe with no clinical toxicity

Adapted from Colucci, European Endocrinology, 2013;9(1):40-7

A very good publication to read

European Thyroid Journal

Translational Thyroidology / Review

Eur Thyroid J 2012;1:88–98
DOI: 10.1159/000339447

Received: March 30, 2012
Accepted after revision: May 3, 2012
Published online: June 27, 2012

Thyroid Hormone Replacement Therapy: Three 'Simple' Questions, Complex Answers

Antonio C. Bianco Sabina Casula

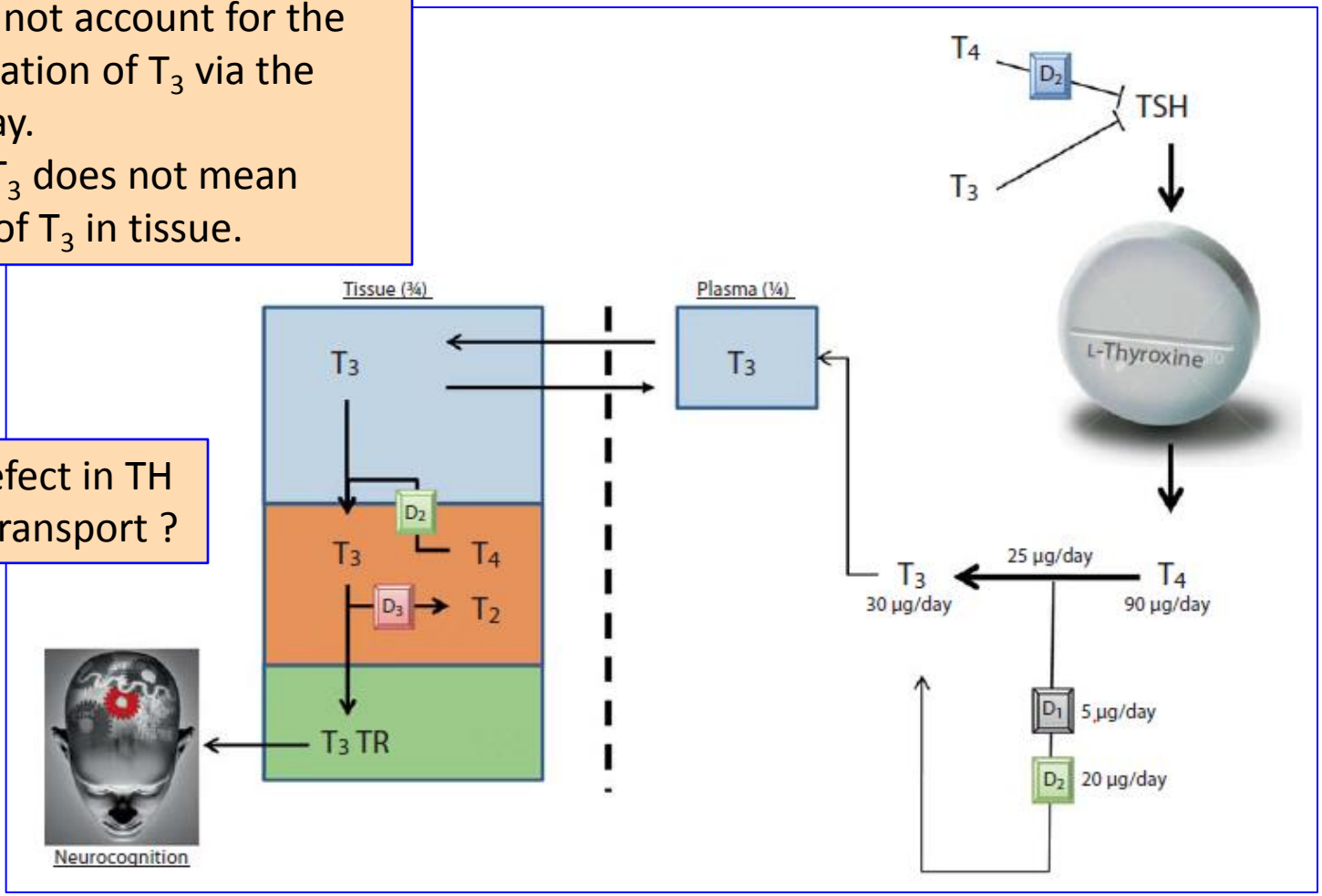
Division of Endocrinology, Diabetes and Metabolism, University of Miami Miller School of Medicine, Miami, Fla., USA

« Despite normalization of serum TSH, FT4 and FT3, about 15% of patients treated with levothyroxine replacement therapy alone do not achieve clinical euthyrodism and experience some level of psychological impairment »

Suppression of TSH is independent of circulating T4

1) Plasma T_3 is a poor predictor of tissue T_3 because it does not account for the production/inactivation of T_3 via the deiodinase pathway.
A normal serum FT_3 does not mean sufficient content of T_3 in tissue.

2) Possible defect in TH metabolism/transport ?



3) What about combined Levothyroxine (T_4) – Liothyronine (T_3) therapy ?

2) History of regulatory requirements for generic products of Levothyroxine by the FDA

- 2000 : Specific guidance for industry for in vivo pharmacokinetic and bioavailability studies with Levothyroxine

- 2007 : Revisions to the monograph for Levothyroxine Sodium tablets in USP 30 (potency)

- 2014 : New product-specific recommendations for Levothyroxine based on the definition of Narrow Therapeutic Index drug (NTI)

The US story

- 1997 : FDA announced that oral drug products containing levothyroxine sodium were considered new drugs subject to approval under the Food, Drug, and Cosmetic Act. At that time, 37 different products on the market with various quality and safety concerns.
- 2000 : FDA issued a specific guidance for industry for in vivo pharmacokinetic and bioavailability studies with Levothyroxine
- 2001 (August) : Deadline for companies to submit applications and get products approval

Guidance for Industry

Levothyroxine Sodium Tablets — In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2000
Clinical Medical

A. Inclusion Criteria

For each pharmacokinetic and bioavailability study outlined below, at least 24 volunteers should complete the trial. The subjects should be healthy volunteers, 18 to 50 years of age and within 15 percent of ideal body weight for their height and build. Sponsors should attempt to enroll an equal number of men and women, if possible. Volunteers recruited for the study should have an acceptable medical history, physical examination, and clinical laboratory tests. All thyroid function tests should be within normal limits. Volunteers with any current or past medical condition that might significantly affect their pharmacokinetic or pharmacodynamic response to levothyroxine sodium should be excluded. Female volunteers should be given a pregnancy test prior to beginning the study. Pregnant women should be excluded from the study. Written informed consent should be obtained from all volunteers before they are accepted into the study.

B. Single-Dose Bioavailability Study

Objective: To determine the bioavailability of the to-be-marketed formulation of levothyroxine relative to a reference (oral solution) under fasting conditions.

Design: The study is a single-dose, two-treatment, two-sequence crossover design. An equal number of volunteers should be randomly assigned to each sequence. The washout period between treatments should be at least 35 days.

Tablet Strength and Dose: A multiple of the highest tablet strength to achieve a total dose of 600 µg should be given to detect T_4 above baseline levels.

Procedure: Following a 10-hour overnight fast, volunteers should be administered a single dose of levothyroxine sodium orally with 240-mL water. The treatments should be as follows:

Typical example : Al-Numani, Int J Clin Pharmacol Ther, 2016; 54: 135-143

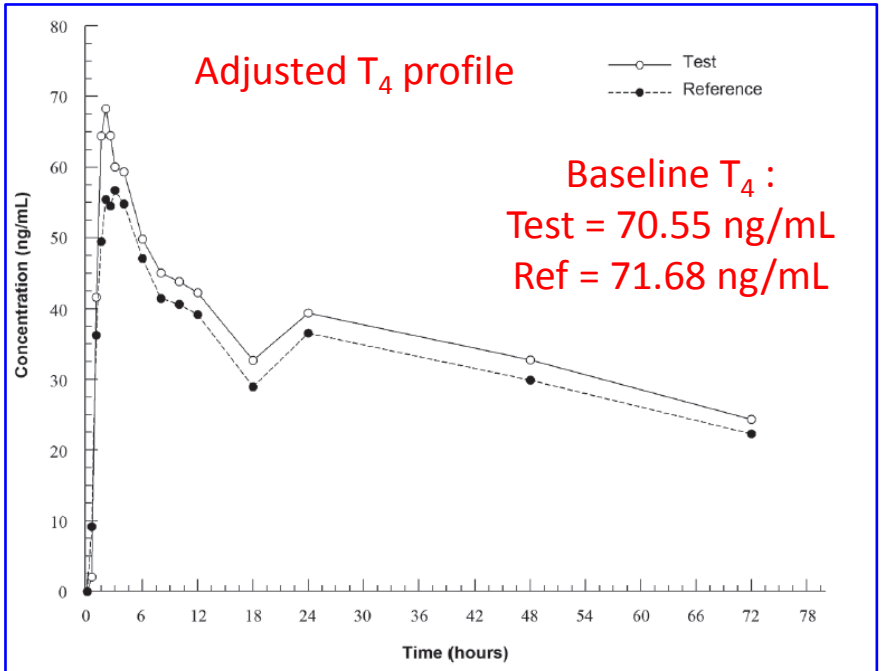


Figure 1. Mean serum concentration versus time profile for baseline-adjusted T_4 for the pharmacokinetic equivalence study (study 1; n = 32).

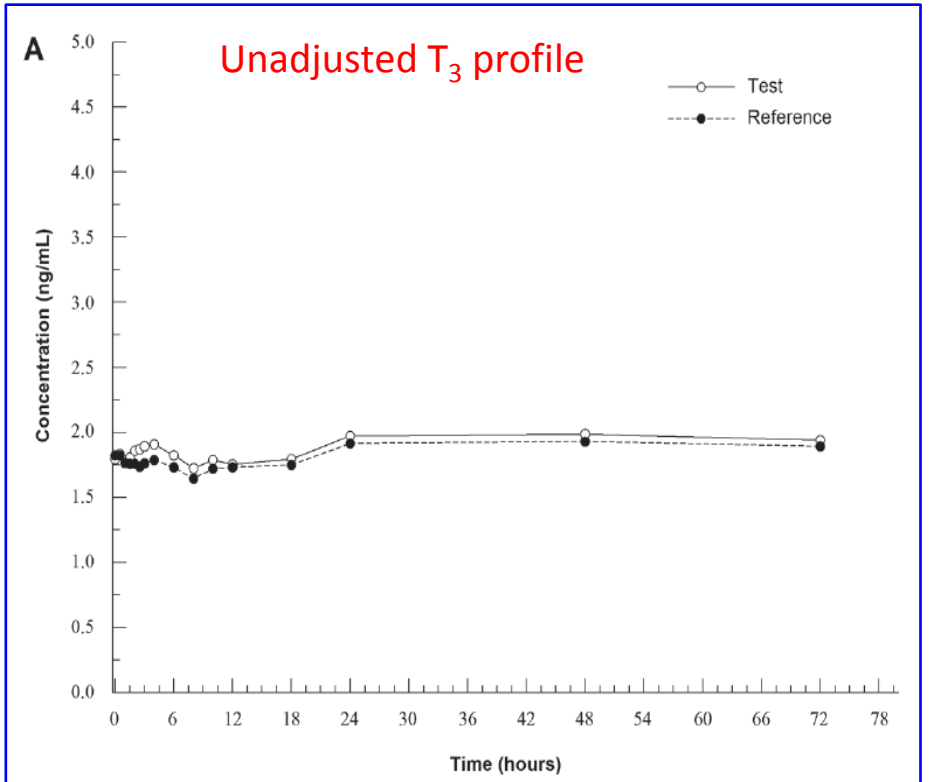


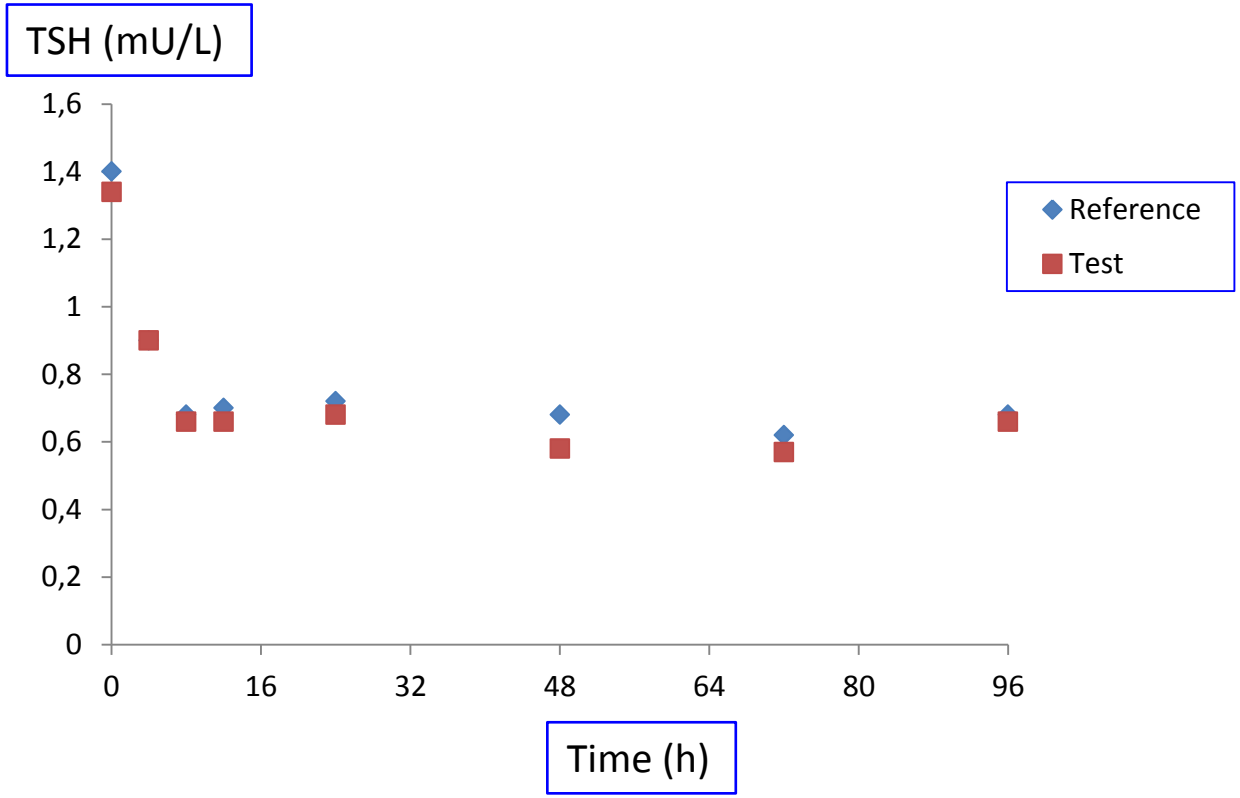
Table 2. Pharmacokinetic equivalence summary statistics and 90% confidence intervals for baseline-adjusted T_4 pharmacokinetic parameters (study 1; n = 32).

Parameter	Geometric mean (range)		Ratio (% test/reference)	90% Confidence Interval
	Test	Reference		
AUC_{0-72} (ng×h/mL)	2,478.4 (1,051.0 – 4,153.0)	2,272.5 (1,021.0 – 3,948.7)	109.06	101.74 – 116.91
C_{max} (ng/mL)	72.75 (31.33 – 126.6)	63.37 (38.60 – 99.23)	114.80	107.36 – 122.76
t_{max} (hours)*	2.00 (1 – 4)	2.00 (1 – 6)	–	–

*Median presented for t_{max}; AUC_{0-72} = area under the concentration-time curve from 0 to 72 hours; C_{max} = maximum concentration; t_{max} = time to C_{max}.

CV_{intra}-%
21.6%
20.8%

Typical mean TSH profiles following a single 600 µg Levothyroxine in healthy subject (personal data with permission)



- TSH is known to respond with logarithmically amplified variation to minor changes in serum FT_4 and FT_3 (Andersen, JCEM, 2002; 87: 1068-1072)
- No safety issue while administering single oral dose of 600 µg Levotyroxine to healthy subjects . From literature, 400 µg and 450 µg doses yield concentrations that are closer to the baseline preventing for an accurate evaluation of the true differences between the two doses.

But still, numerous issues remained …

- Clinicians expressed concerns about substitution of one product for another
- 2005 : FDA co-sponsored a meeting with the American Thyroid Association, the Endocrine Society, and the American Association of Clinical Endocrinologists to discuss concerns
- Evidence that the concept of bioequivalence was not well understood

Illustration of misunderstood concept of bioequivalence …

Irwin Klein, M.D.
Professor of Medicine and Cell Biology
NYU School of Medicine
Chief, Division of Endocrinology
North Shore University Hospital

Evaluation of Bioequivalence and Efficacy of L-thyroxine Preparations in the Treatment of Human Thyroid Disease

7 February 2003

6. BIOAVAILABILITY

Under current standards for bioequivalence of T_4 formulations, treatment doses of T_4 are considered approvable and equivalent if the patient exposure falls within 80%-125% of the dose administered as a solution of an equivalent T_4 dose.[26] While this equivalence is only tested at a single 600 mcg dose in normal healthy volunteers, the standard is applied across all dosage strengths. According to this rationale, current standards call for the equivalency doses that are 80%-125% of the label as reflected below.

L-thyroxine Bioequivalence and Efficacy
Irwin Klein, M.D.
7 February 2003

This potential variance in the effective dosage which is attributable to acceptable bioequivalence ranges is unknown (since direct comparative T_4 bioequivalence studies are not required) and not disclosed to the practitioner. The adverse effects of this variance are borne by the patient who might be prescribed for example a 100 mcg dose of T_4 and actually receive a range of doses from 80 mcg to 125 mcg, encompassing as many as 4 labeled dose levels. This variance with the attendant changes in serum TSH levels can lead to chemical hyperthyroidism and the risk of atrial fibrillation or hypothyroidism and unwanted symptoms, altered lipid levels or cardiac contractility and accelerated atherosclerosis.[4,21,27] As a result, the patients may well require repeated dose adjustments to restore TSH to normal if the drug preparation (brand) is changed.

Not better in Europe, at least in France …

afssaps
Agence française de sécurité sanitaire des produits de santé

REPUBLIQUE FRANÇAISE

20 mai 2010

Lettres aux professionnels de santé

Recommandations sur la substitution des spécialités à base de lévothyroxine sodique

Information destinée aux médecins généralistes, endocrinologues, gynécologues, pédiatres et internistes.

Madame, Monsieur,

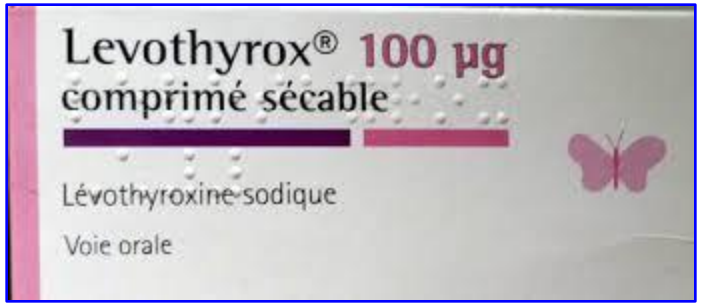
L'Agence française de sécurité sanitaire des produits de santé (Afssaps) souhaite porter à votre connaissance les informations suivantes sur la substitution des spécialités de lévothyroxine sodique récemment inscrites au répertoire des médicaments génériques[1] dont la spécialité de référence est Lévothyrox®.

La lévothyroxine sodique est indiquée dans le traitement des hypothyroïdies et dans les circonstances, associées ou non à une hypothyroïdie, où il est nécessaire de freiner la TSH.

- In case of substitution from Brand to Generic, from Generic to Brand or from Generic to an other Generic, then a TSH blood test is required within 6 to 8 weeks of the substitution.

Opponents : no savings from the substitution

1)



Brand : 2 €/ month – 30 tablets
Generic : 1.5 €/ month – 30 tablets
Gain : 0.5 €

2)

+

Blood collection : 3.8 €
TSH Blood test : 8.1 €

Medical examination : 25 €

Total clinical monitoring : 11.9 €

Net cost of the substitution = 11.4 €

2) Potency specifications for Levothyroxine sodium

- Levothyroxine degrades quickly with exposure to light, moisture, oxygen, and carbohydrate excipients
- These conditions typically occur during levothyroxine formulation, tableting, packaging, and storage
- Many products were manufactured using an overage
- Up to 2007 : allowed potency range of 90% – 110%
- Since 2007 : FDA requires new potency range : 95% – 105%
- Same requirements in Europe but sometimes 90% - 105%

2007 : Revision of the monograph for Levothyroxine sodium

DEPARTMENT OF HEALTH & HUMAN SERVICES

OCT 3 2007

Ms. Angela G. Long
Executive Secretariat
The United States Pharmacopeial
Convention, Inc.
12601 Twinbrook Parkway
Rockville, MD 20852

Food and Drug Administration
Rockville MD 20857

REF: 10-07-001-O

Dear Ms. Long:

This letter proposes revisions to the monograph for Levothyroxine Sodium Tablets in USP 30, pages 2470-2471.

We propose that the assay range specification in the USP monograph for Levothyroxine Sodium Tablets be narrowed from the current 90 percent to 110 percent of label claim to 95 percent to 105 percent of label claim. This proposal is part of an ongoing effort to address concerns expressed about the performance of approved levothyroxine sodium products and to help ensure that levothyroxine sodium drug products maintain their quality throughout their shelf-lives.

In response to physician and patient concerns about product performance, particularly for patients taking different levothyroxine sodium products after prescription refills that may involve products from different manufacturers, we requested product stability data from manufacturers of all the approved, marketed levothyroxine sodium drug products manufactured between July 2003 and June 2005 to obtain a stability profile for each marketed levothyroxine sodium product. Although all approved levothyroxine sodium products meet the current potency specifications, it is evident from these data that there is

Levothyroxine : a « critical strength » drug ?

Contains Nonbinding Recommendations

Draft Guidance on Levothyroxine Sodium

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Levothyroxine sodium

Dosage Form; Route: Tablet; oral

Recommended Studies: One study

1. Type of study: Fasting
   Design: Single-dose, four-way, fully replicated crossover in vivo
   Strength: 0.3 mg
   Subjects: Healthy males and non-pregnant females, general population
   Additional comments:
   1. Females should not be pregnant or lactating, and should practice abstention or use appropriate forms of contraception during the study.
   2. Levothyroxine has a long elimination half-life, hence adequate washout periods should be ensured between treatments in the crossover study. Measurement of levothyroxine may be truncated to 48 h post-dose.
   3. The dose for R and T administered during the study should be 0.6 mg to ensure adequate measurement of the analyte.
   4. Given the numerous drug-drug interactions for levothyroxine sodium, caution should be exercised in administering concomitant medications during the study.
   5. Post-dose levothyroxine measurements by the baseline levothyroxine value should be corrected in each period for each subject. The baseline value should be obtained from the average of three levothyroxine measurements taken before dosing (i.e., at 0.5 h, 0.25 h, and 0 h pre-dose).
   6. Applicant may consider using the reference-scaled average bioequivalence approach for levothyroxine sodium.

Analytes to measure (in appropriate biological fluid): Levothyroxine in serum

Bioequivalence based on (90% CI): Baseline-corrected levothyroxine

Waiver request of in vivo testing: 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.137 mg, 0.15 mg, 0.175 mg, and 0.2 mg based on: (i) an acceptable bioequivalence study on the 0.3 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

Regulatory Filing Recommendations: Note that there are five different reference listed drug (RLD) products for levothyroxine sodium tablets. A separate fasting bioequivalence study (and a

Recommended Dec 2014

2014 New product-specific recommendation for Levothyroxine sodium

- Strength : 0.3 mg (no more requirement for dose proportionality : 3 x 200 µg and 6 x 100 µg and 24 x 25 µg tablets)
- Reference-scaled average bioequivalence approach based on the definition of NTI drug

FDA conditions to declare Levothyroxine as a NTI drug

Explanation: FDA has concluded that levothyroxine sodium is a narrow therapeutic index (NTI) drug based on the following evidence:

- The range between serum levothyroxine therapeutic and toxic concentrations is narrow;
- Some levothyroxine-associated toxicities are serious and/or irreversible;
- Sub-therapeutic levothyroxine concentrations result in inadequate treatment and lead to poor clinical outcomes;
- Levothyroxine sodium requires individual dose titration to achieve a satisfactory balance between maximizing efficacy and minimizing serious dose-related toxicity;
- Therapeutic drug monitoring based on serum TSH and total or free-T_4 levels is routinely employed to facilitate levothyroxine dose titration; and
- Levothyroxine has small-to-medium within-subject variability.

The study design should be a fully replicated crossover approach in order to

- Scale bioequivalence limits to the variability of the referenced product; and
- Compare test and referenced product within-subject variability.

For details about Method for Statistical Analysis Using the Reference-Scaled Average Bioequivalence Approach for narrow therapeutic index drugs, refer to the draft Guidance on Warfarin Sodium.

FDA conditions for Levothyroxine-NTI drug are debatable …

Explanation: FDA has concluded that levothyroxine sodium is a narrow therapeutic index (NTI) drug based on the following evidence:

- The range between serum levothyroxine therapeutic and toxic concentrations is narrow; **NO**
- Some levothyroxine-associated toxicities are serious and/or irreversible; **YES**
- Sub-therapeutic levothyroxine concentrations result in inadequate treatment and lead to poor clinical outcomes; **NOT necessarily and the reverse is also true**
- Levothyroxine sodium requires individual dose titration to achieve a satisfactory balance between maximizing efficacy and minimizing serious dose-related toxicity; **YES**
- Therapeutic drug monitoring based on serum TSH and total or free-T_4 levels is routinely employed to facilitate levothyroxine dose titration; and **YES for TSH, never for Total T4**
- Levothyroxine has small-to-medium within-subject variability. **YES**

The study design should be a fully replicated crossover approach in order to

- Scale bioequivalence limits to the variability of the referenced product; and
- Compare test and referenced product within-subject variability.

For details about Method for Statistical Analysis Using the Reference-Scaled Average Bioequivalence Approach for narrow therapeutic index drugs, refer to the draft Guidance on Warfarin Sodium.

MHRA

Levothyroxine Tablet Products:
A Review of Clinical & Quality Considerations

07 January 2013

According to the MHRA,
« Levothyroxine does not fulfil the criteria for being a NTI drug. However, there is evidence that in at least some patients, precise dosing over the long-term is critical ».

1 Lay Summary

Over the past five years MHRA has received an increase in the number of reports from healthcare professionals and patients raising concerns about potential inconsistencies in the quality and effectiveness of different makes of levothyroxine products and even between different batches of the same product. Starting in January 2011, the MHRA has reviewed the medical and scientific literature to assess whether there could be differences in the bioavailability (extent / rate of absorption) of levothyroxine between different tablet products and/or batches, what clinical implications this may have and whether additional controls were needed. This report is a summary of this review which was endorsed by the Commission on Human Medicines, an independent panel of experts who advise the licensing authority.

Proposed NTI Drug Definition

- Those drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions. Serious events are those which are persistent, irreversible, slowly reversible, or life-threatening. NTI drugs generally have the following characteristics:
  - Steep dose-response curves for both safety and efficacy in the usual dosing interval or close effective concentrations and concentrations associated with serious toxicity,
  - Subject to therapeutic drug monitoring based on pharmacokinetic (PK) or pharmacodynamic (PD) measures, and
  - Generally small within subject variability.

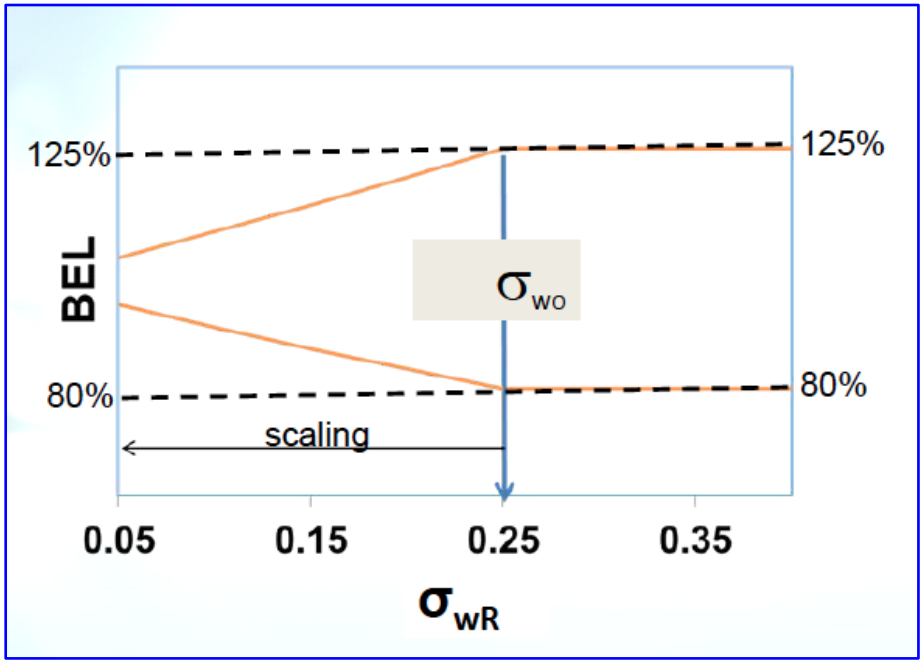
Coefficient of Variation (CV) for NTI Drugs

Summary of Residual Variability (% CV) from ANDAs reviewed between 1996-2008

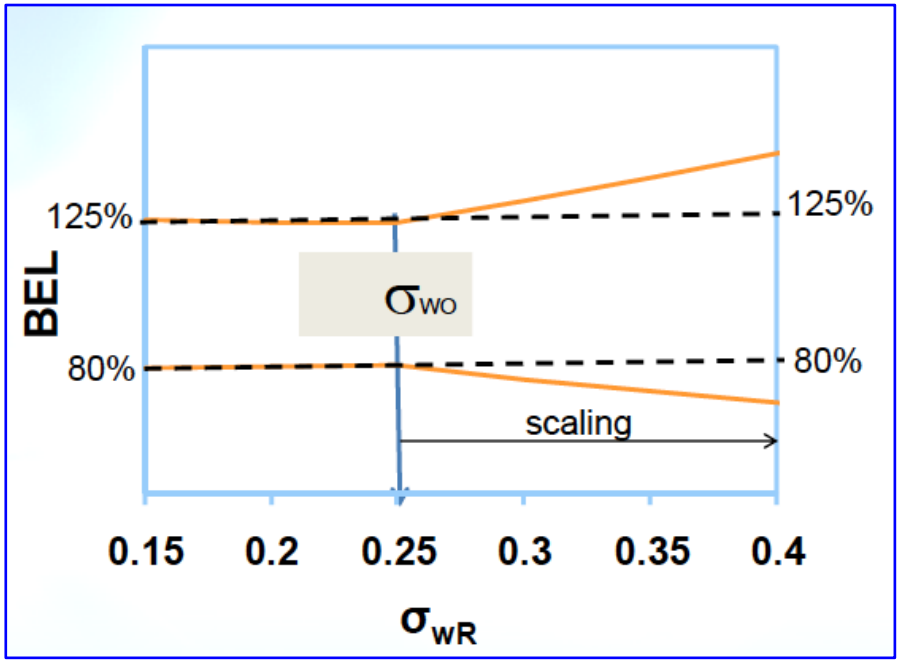
	AUC_{0-t}		C_{max}	
Drugs	**Mean**	**Range**	**Mean**	**Range**
Warfarin (n=29)	5.7	3.3, 11.0	12.7	7.7, 20.1
Levothyroxine (n=9)	9.3	3.8, 15.5	9.6	5.2, 18.6
Carbmazepine (n=15)	8.0	4.4, 19.4	8.7	5.2, 17.6
Lithium Carbonate (n=16)	7.8	4.5, 14.0	13.5	6.4, 24.4
Digoxin (n=5)	21.7	13.1, 32.2	21.0	14.3, 26.1
Phenytoin (n=12)	9.2	4.1, 18.6	14.9	7.4, 20.0
Theophylline (n=3)	17.9	12.8, 24.2	18.2	11.8, 25.8

Not a comprehensive list of NTI drugs

Novel bioequivalence approach for narrow therapeutic index drugs



Pictorial representation of scaling in BE for NTIs



Pictorial representation of scaling in BE for HVDs

From Kamal Midha et al, ACPS-CP meeting Washington 26 July 2011

For details of statistical analyses, see :

- Draft Guidance on Warfarin Sodium - December 2012http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm201283.pdf

- Study design : 4-way, fully replicated crossover design
- 4 steps :
  - 1) Determine the within-subject standard deviation (SD) of the reference product for the pharmacokinetic parameters AUC and Cmax. Do as well for the test product.
  - 2) Use the referenced-scaled procedure to determine BE for individual PK parameter(s).
  - 3) Use the unscaled average bioequivalence procedure to determine BE for individual PK parameter(s). Every study should pass the scaled average bioequivalence limits and also regular unscaled bioequivalence limits of 80.00-125.00%.
  - 4) Calculate the 90% confidence interval of the ratio of the within subject standard deviation of test product to reference product.

Two conditions to declare bioequivalence : Means and Variances

Scaled Average BE

- scaled average BE criterion

Means → $$\frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} \leq \theta$$ ← Variance

- θ defined as

$$\theta = \frac{[\ln(\Delta)]^2}{\sigma_{W0}^2}$$ ← Fixed by Authorities ← Fixed by Authorities

FDA proposals : $\Delta = 1.111$ and $\sigma_{W0} = 0.10$

$$\Theta = \exp\left[\pm (\ln \Delta)\, \sigma_{WR}\right) / \sigma_{W0}]$$

- Acceptance range (AR) for Levothyroxine :
  - CV-% = 5.2% or $\sigma_{WR} = 0.0519$ then AR = [94.68 – 105.62]
  - CV-% = 9.6% or $\sigma_{WR} = 0.0958$ then AR = [90.41 – 110.61]
  - CV-% = 10.0% or $\sigma_{WR} = 0.0997$ then AR = [90.00 – 111.11]
  - CV-% = 15.0% or $\sigma_{WR} = 0.1491$ then AR = [85.47 – 116.99]
  - CV-% = 18.6% or $\sigma_{WR} = 0.1844$ then AR = [82.36 – 121.42]
  - CV-% = 21.42% or $\sigma_{WR} = 0.2118$ then AR = [80.00 – 125.00]

Sample size according to the classification of Levothyroxine by the Authorities

Conditions : α = 5% , ß = 20% , GMR between 95-105%

CV-%	No NTI : Standard AR 80.00% – 125.00%	NTI : Narrow AR 90.00% - 111.11%	NTI : Reference-scaled AR
5.2%	12 (minimum)	14	[94.68 – 105.62] # no solution
9.6%	12 (minimum)	38	[90.41 – 110.61] 24, could be less
18.6%	16	134	[82.36 – 121.42] 24
	UK; NL ; … ?	F, … ?	USA

Comparison of variances : decision rule = upper limit of the 90% CI < 6.25 (2.5 for SD)

- Arbitrary limit but judged reasonable by the FDA
- Could anticipate the situation of Reference vs Reference to be bioequivalent
- What consequence for the estimation of sample size ?

Generic drug of Levothyroxine tablet : NTI drug or not ? Could be a topic on the agenda of the third edition of the Global Bioequivalence Harmonisation Initiative

23-24 March 2015, Amsterdam, Netherlands