Endogenous Substance Bioavailability and Bioequivalence:
Levothyroxine Sodium Tablets

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Overview

- Background:
  - Why levothyroxine sodium tablets were declared a “new drug”
  - “Guidance for Industry”

- FDA’s decision for bioequivalence evaluation of levothyroxine sodium tablets:
  - Study design
  - Bioequivalence analyses

Introduction

- Prior to August, 2000, levothyroxine sodium was an unapproved marketed drug (“grandfathered”)

- Introduced in the 1950s

  (more pure, synthetic form of Thyroid, USP)

- In 1997 at least 37 manufacturers or re-packagers of levothyroxine sodium tablets

Introduction - *cont.*

- Although the clinical effectiveness of levothyroxine sodium had been established through four decades of clinical use, there was a high degree of uncertainty about all of the products. Namely, issues existed with regard to:
  - Product stability (i.e., shelf-life);
  - Formulation consistency over time within a given “brand;” and
  - Bioequivalence had never established between brands.

Product Stability

- Levothyroxine degrades quickly with exposure to light, moisture, oxygen, and carbohydrate excipients
- Between 1990 and 1997:
  - 10 recalls, 150 lots, and 100 million tablets
    - content uniformity, sub-potency, and stability failures
- Many products were manufactured using an overage

PRODUCT	% of LABELED CLAIM
Flint (Synthroid™)	106% – 109%
USV	101%
Geneva – Zenith	93% – 108%
Rugby	107%

Fish et al. (1987)

Formulation Consistency

- Significant changes in formulation were occurring over time as firms attempted to improve product stability.
- Case reports in the literature suggesting that therapeutic failures had occurred when patients received a refill of the same product for which they had been previously stable.
- Of the 58 case reports of therapeutic failure received by the Agency, from 1987 - 1994, nearly half occurred when patients received a refill of a product on which they had been stable for years.

Federal Register Notice (62 FR 43535)

- In an effort to standardize levothyroxine sodium tablets, and to reduce the instances of therapeutic failures, on August 14, 1997, the FDA declared levothyroxine sodium tablets a “new drug”

- Sponsors wishing to continue to market their product needed to submit an NDA or file a citizen’s petition describing why an NDA was not necessary

FDA Guidance for Industry

Levothyroxine Sodium Tablets - *In Vivo* Pharmacokinetic and Bioavailability Studies and *In Vitro* Dissolution Testing -- Feb. 2001

- Introduction and Background
- *In vivo* pharmacokinetic and bioavailability studies
  - Inclusion criteria
  - Single-dose (relative) bioavailability
  - Dosage-form proportionality
- *In vitro* dissolution testing
- Formulation
- Biowaiver
- Assay validation

Relative Bioavailability

Objective - determine the relative BA of the proposed formulation to a reference oral solution - fasting

Design - single-dose, 2 treatment, 2 sequence crossover design with a washout interval of at least 35 days

Dose - a total dose of 600 mcg

- Treatment 1: 2 x 300 mcg levothyroxine tablets
- Treatment 2: an oral solution equal to the dose in treatment 1

Analyses - AUC and C_{max} without baseline correction (T_4)

Dosage-form Proportionality

Objective - determine the dosage-form proportionality among the to-be-marketed strengths - fasting

Design - single-dose, 3 treatment, 6 sequence crossover design with a washout interval of at least 35 days

Dose - multiples to achieve a total dose of 600 mcg

- Treatment 1: 12 x 50 mcg
- Treatment 2: 6 x 100 mcg
- Treatment 3: 2 x 300 mcg

Analyses - AUC and C_{max} without baseline correction (T_4)

Formulation

- Must target 100% of label claim
- No unaccountable or “stability” overages

NDAs

- Between June 1999 and July 2001, nine sponsors submitted “stand alone” NDA applications
- The first product was approved in August, 2000
- There are currently six approved levothyroxine sodium tablet NDAs

Approved Applications

Sponsor	IND #	NDA #	IND Filed	NDA Filed	NDA Review
Lloyd, Inc.	57,315	21-116	11-20-98	08-19-99	AP (10-24-02)
Jerome Stevens	57,252	21-210	11-05-98	10-19-99	AP (8-21-00)
Genpharm	59,041	21-292	09-24-99	06-27-00	AP (5-31-02)
Jones (King)	59,177	21-301	10-26-99	07-28-00	AP (5-25-01)
MOVA	54,672	21-342	11-26-97	04-30-01	AP (3-01-02)
Abbott	62,720	21-402	06-06-01	07-31-01	AP (7-24-02)

Abbott Laboratories

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The FDA's decision for the evaluation of levothyroxine sodium tablet bioequivalence

Study design

Bioequivalence analyses

Data Limitations

- Their data was confirmatory and useful when the FDA adopted a baseline correction method for evaluating levothyroxine sodium tablet bioequivalence

- However, baseline correction has some drawbacks related to the lower doses used in the study:
  - 400 mcg and 450 mcg doses yield concentrations that are closer to the baseline
  - prevents an accurate evaluation of the true differences between the 400 mcg and 450 mcg doses
  - doses of 600 mcg or greater should be utilized, as suggested in the bioequivalence study protocol

Protocol for Evaluating BE

Objective - determine if bioequivalence can be conferred between Product A and Product B - fasting

Design - single-dose, 2 treatment, 2 sequence crossover design with a washout interval of at least 35 days

Subjects - healthy male and female subjects

Dose - multiples to achieve a total dose of 600 mcg

- Test Product: 2 x 300 mcg tablets
- Reference Product: 2 x 300 mcg tablets

Analyses - AUC and C_{max} with a baseline correction (T_4)

Biowaiver - strengths not studied *in vivo*

Healthy Volunteers

- Allows for the use of a single dose study
- More sensitive evaluation of true formulation differences between products
- Single-dose study cannot be conducted in patients

Dose

- The 600 mcg dose in healthy subjects provides concentrations that are significantly higher than the individual subject's baseline T_4 value

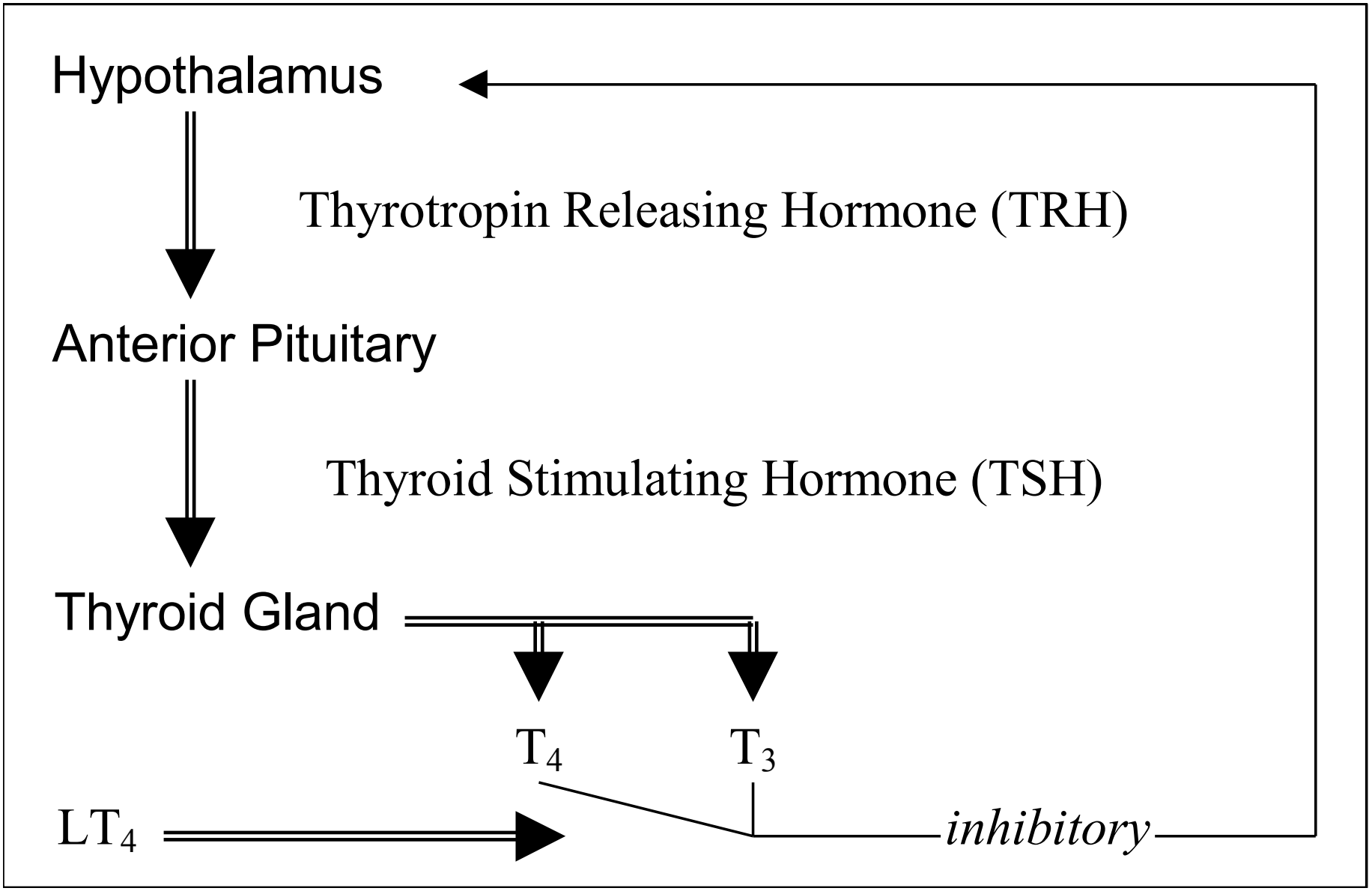
- The issue of non-linearity is not an issue since the subject is receiving the same amount of drug in each treatment period

T_4, T_3, and TSH

- T_4 (LT_4) is the preferred measure for demonstrating bioequivalence - it can be accurately measured *in vivo* and is the drug that is being administered to the subject

- T_3 is an active metabolite

- TSH is a biomarker that is an indirect measure and is "downstream" from what is being administered and is considerably more variable than T_4


Hypothalamus
Thyrotropin Releasing Hormone (TRH)
Anterior Pituitary
Thyroid Stimulating Hormone (TSH)
Thyroid Gland
T4
T3
LT4
inhibitory

21 CFR 320.24(b)

- … descending order of accuracy, sensitivity, and reproducibility, … for determining bioavailability and bioequivalence of a drug product.

  - (1)(i) … concentration of the active ingredient … in blood, plasma, serum, … (T_4)
  - (2) … urinary excretion of the active moiety ...
  - (3) … acute pharmacological effect of the active moiety … (TSH)
  - (4) Well controlled clinical trial … (TSH)
  - (5) … in vitro testing
  - (6) Any other approach deemed adequate by FDA

Bioequivalence Analysis

- Using total T_4, without a baseline correction, is insensitive for bioequivalence analysis

- A baseline correction, whereby the mean of 3 pre-dose samples are subtracted from all subsequent post-dose values *, is preferred

* data provided by Abbott Laboratories

Total T_4 Adjusted for Baseline (Ratios of LSM – 90% Confidence Intervals)

[data from dosage-form equivalence studies]

Product	$AUC_{0\text{-}48\ hrs}$		C_{max}	
	A vs. B	C vs. B	A vs. B	C vs. B
1	102.4% (94.7% - 110.8%)	100.2% (92.6% - 108.4%)	103.5% (97.3% - 110.0%)	97.7% (91.8% - 103.8%)
2	103.72% (95.98% - 112.09%)	91.45% (84.70% - 98.74%)	103.12% (96.87% - 109.76%)	95.05% (89.36% - 109.76%)
3	104% (97.09% - 110.35%)	98% (92.36% - 104.92%)	102% (94.94% - 108.57%)	100% (92.79% - 106.04%)
4	97% (90% – 105%)	114% (106% - 123%)	94% (87% - 101%)	104% (97% - 111%)

Treatment A = 12 x 50 mcg; Treatment B = 6 x 100 mcg; Treatment C = 2 x 300 mcg

Conclusion

- The FDA has thoroughly reviewed each NDA submission, the literature, and the recent “correction method” study and concludes the following:

  – Levothyroxine can be evaluated in healthy subjects
  – A single-dose crossover study design is preferred
  – T_4 is an appropriate and sensitive measure
  – A baseline correction using the mean of 3 pre-dose samples is adequate when determining equivalence between two levothyroxine sodium products

Dr. Barbara Davit