

Clinical Perspectives on Levothyroxine Sodium Products

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Overview of Presentation

- **Thyroid physiology, disease states, uses of levothyroxine sodium products**
- **Current issues surrounding approved LT4 products**

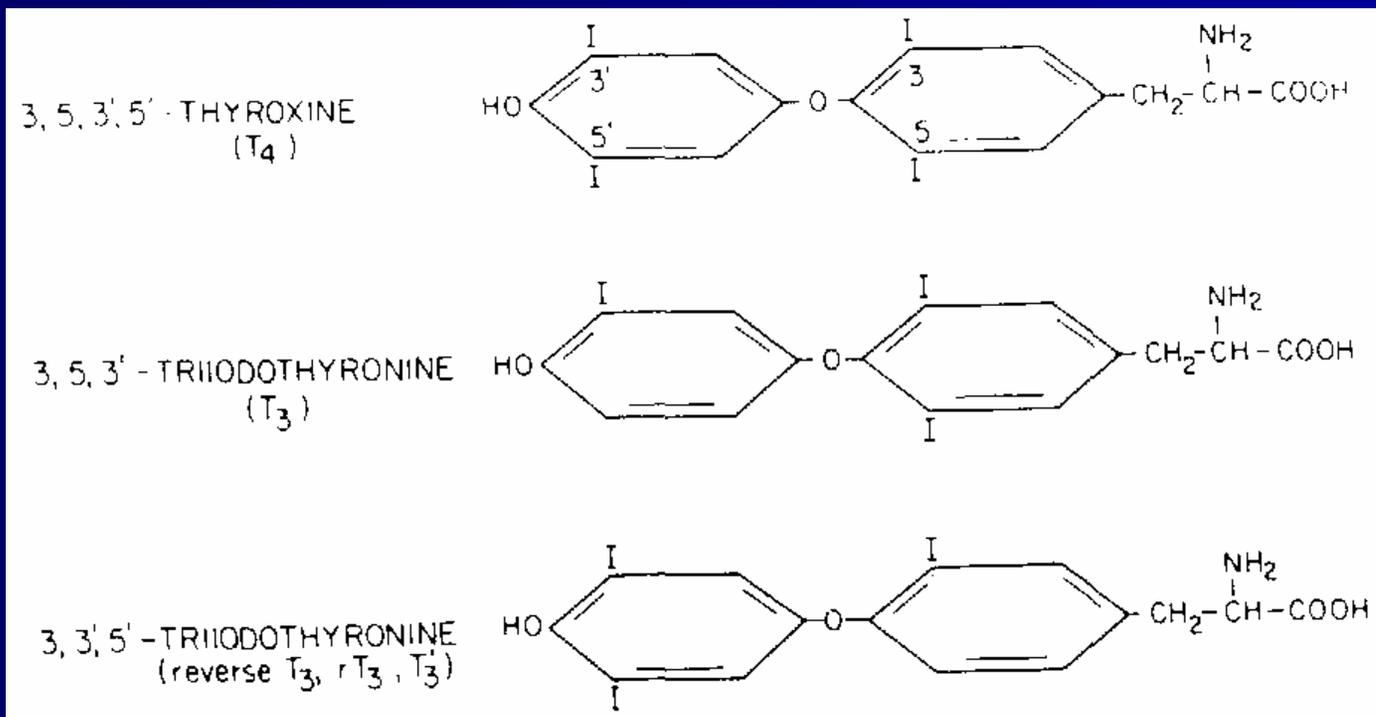
Introduction

- **Levothyroxine (LT4) sodium is the sodium salt of the levo-isomer of the thyroid hormone, thyroxine**
- **Widely prescribed for:**
 - Treatment of hypothyroidism
- **Other clinically important uses**
 - Treatment of differentiated thyroid cancer
 - Suppression of thyroid nodules
- **Estimated > 13 million patients treated w/ LT4 in the U.S.**

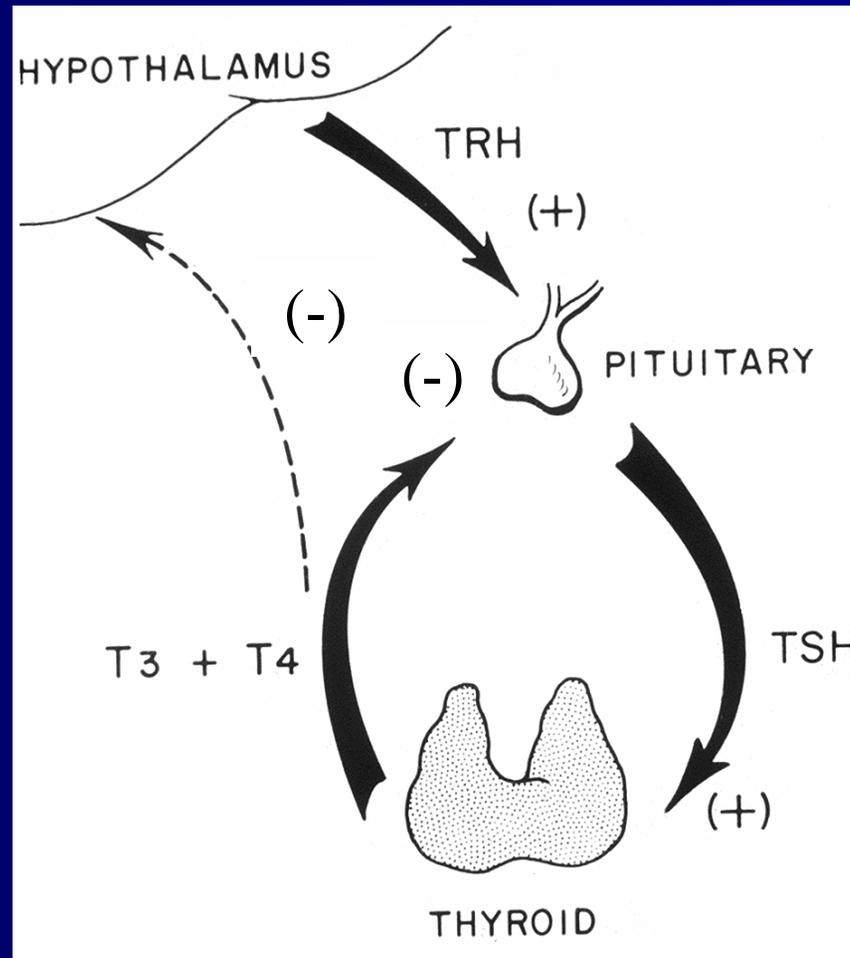
Thyroid Physiology

- **Thyroid gland**
 - Located anteriorly in the neck
 - Secretes thyroid hormone – majority as the prohormone T4, some active T3 secreted but most all derived from peripheral conversion
- **Sequential removal of iodine atoms from T4 by deiodinase enzymes to form primarily**
 - Active T3
 - Inactive reverse T3

Structure of Thyroid Hormones



Hypothalamic-Pituitary-Thyroid Axis Physiology



Effects of Thyroid Hormone

- **Diverse effects at the cellular, tissue, and organ level**
- **Essential for growth and development, maintaining hemodynamic stability, and overall metabolic homeostasis. Examples:**
 - **General: body temperature regulation, weight maintenance**
 - **Cardiovascular system: affects contractility, cardiac output, lipid metabolism**
 - **Neuromuscular system: can affect mentation, muscle strength/tone**
 - **GI: transit time**
 - **Renal system: affects free water clearance**
 - **Reproductive system: fertility, menstrual cycles**
 - **Skin/appendages: hair, skin, and nail integrity**
 - **Pregnancy – neurologic development of the fetus**

Disease States

- **Pathologic states can result from:**
 - **Insufficient thyroid hormone activity**
 - Most due to primary thyroid gland failure secondary to autoimmune destructive process
 - Other causes include surgery, infection, radioablation, drug-induced, infiltrative processes, pituitary diseases
 - **Excessive thyroid hormone activity**
 - Most commonly due to autoimmune process
 - Other causes include toxic nodules, thyroiditis, factitious, very rare pituitary tumors

Clinical Presentation

- Can be variable and non-specific, seemingly benign
- Even mild hypo- or hyperthyroidism may result in significant morbidity or adverse consequences
 - e.g., subclinical hyperthyroidism can increase the risk of osteoporosis and arrhythmia; subclinical hypothyroidism associated with dyslipidemia and possible diastolic dysfunction
- Clinical consequences of insufficient/excess TH activity must therefore be considered in the management of thyroid disorders with thyroid hormone

Thyroid Hormone Therapy

- **In use for over 100 years**
 - **1891 – Murray treated a myxedematous patient with sheep thyroid extract and noted clinical improvements**
 - **Dessicated thyroid extract of animal origin containing both T4 and T3 used in first ½ of 20th century. Amount of T3 often higher than that secreted by human thyroid gland resulting in hyperthyroidism in many cases**
 - **Synthetic TH as LT4 became available in 1950s (not under FDA-approval)**

Thyroid Hormone Therapy cont'd

- **LT4 undergoes T4 to T3 conversion enabling active hormone activity; lower risk of hyperthyroidism than desiccated TH products**
- **Improvements in laboratory assays to assess thyroid function allowed for better dose selection.**
- **Laboratory tests to follow:**
 - **Free T4 (or Free T3)**
 - **TSH**
 - **Sensitive TSH assays w/ lowest reliable measurements of 0.02 mIU/L or less**

Uses for Thyroid Hormone

- **Replacement of deficiency states**
 - Adult dose ~1.6 mcg/kg/day,
 - Special populations require careful dose consideration: elderly, cardiac patients, pregnancy, children
 - Target TSH within “normal” range and free T4 in upper range of normal and adjust dosing to ensure clinical s/sxs improve
- **Suppression of TSH in thyroid cancer**
 - Treatment aimed at suppressing TSH stimulation of thyroid tissue growth
 - Targeting more narrow range of TSH
 - High risk patients target TSH <0.1; low risk target TSH at or below the lower limit of nl (0.1 – 0.5 mIU/L)
- **Thyroid nodule suppression**

Dosing Considerations

- **Suboptimal dosing can result in insufficient or excessive thyroid hormone activity placing the patient at risk of the clinical consequences**
- **Necessary to dose adjust to achieve therapeutic goal. Particularly relevant in vulnerable patient population**
 - **Elderly**
 - **Pediatric**
 - **Pregnancy**
 - **Thyroid cancer – suboptimal may result in cancer recurrence**
- **Given the importance of precise dosing and the need for routine laboratory monitoring to avoid the clinical consequence of over- or under-treatment, LT4 is considered a drug with a narrow therapeutic index by many in the scientific community**

Current Issues

- **May 2005 joint public meeting held between FDA, ATA, AACE and Endocrine Society to discuss concerns regarding bioequivalence testing between LT4 products**
- **Assertion made that two products approved by FDA as bioequivalent might differ from one another in potency by 12.5% but one product might still be substituted for another despite this difference in potency**

FDA Approved L-T4 Doses

These are changes that clinicians make deliberately every day!

% Increase		50	17	14	12	12	10	10	17	14
Dose, μg	50	75	88	100	112	125	137	150	175	200
% Decrease	-33	-15	-12	-11	-10	-9	-9	-14	-13	

 Difference of <25%

 Difference of <12.5%

Current Issues

- **Concern *within* a product**
 - **Does stability for an individual product over its labeled shelf-life vary such that there is loss of potency that can result in a patient one day taking 125 mcg but over time, in that same product, the amount of active ingredient is reduced to 112 mcg?**
 - **Could there be sufficient variability in stability within an individual product that the amount of active ingredient differs significantly from refill to refill?**

Conclusion

- **Management of thyroid disorders and the quality of current LT4 products have advanced significantly over the past several decades.**
- **Are the current standards for approval adequate to ensure that these products are safe and effective for use by over 13 million patients?**

