Hypothyroidism Therapeutics PHAR 451

Peter Loewen, B.Sc.(Pharm), ACPR, Pharm.D., FCSHP
Lower Mainland Pharmacy Services
Vancouver General Hospital
University of British Columbia

Remember?

1. The metabolically active thyroid hormone is _____.
2. The main stimulus for release of this hormone is _____.
3. The most common cause of hypothyroidism is _____.
4. The most important lab test for detecting hypothyroidism and monitoring drug therapy is _____.

Objectives

After the session, and upon personal reflection and study, students will be able to

1. Rationalize a diagnosis of hypothyroidism on the basis of signs and symptoms combined with biochemical tests.
2. Design, implement and monitor (efficacy/toxicity) an effective pharmacotherapeutic plan for managing primary hypothyroidism.
3. Identify and manage common drug related-causes of hypothyroidism.

Case

- 70 y/o F presents to your pharmacy, accompanied by her daughter
- Appearance: pale, tired, dry skin.
- Rx: Synthroid 125 mcg qd.

- PMH: HTN, CAD (MI '03), osteoarthritis
- Medications on profile:
  - ASA 325 mg/d, HCTZ 25 mg/d, metoprolol 100mg/d
  - Also takes: acetaminophen 4g/d, $CaCO_3$ (1500 mg/d elemental Ca)

Case

- Labs:
  - TSH 56 (0.5 - 5.0 μU/mL)
  - fT3 1.4 (3.5-7.7 pmol/L)
  - fT4 5.0 (9-25 pmol/L)
  - Lytes: Na 131, others N
- Vitals:
  - HR 50, BP 135/90, Temp N, RR 25

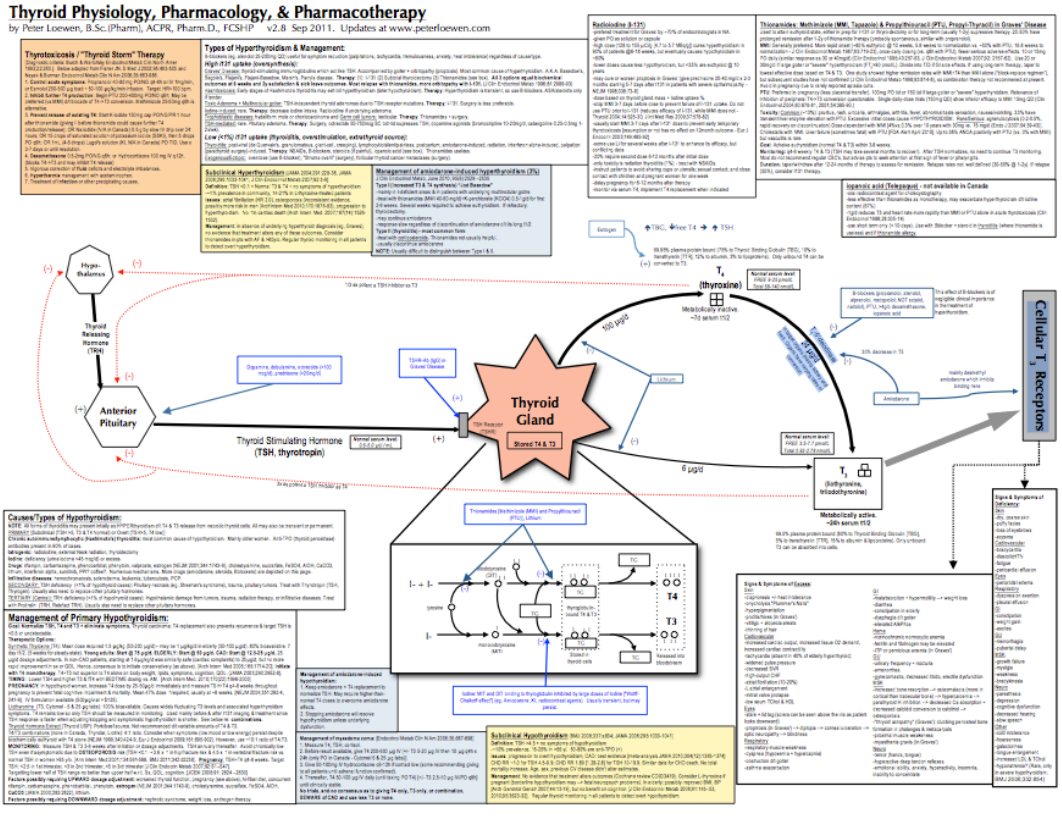
- What do you think this lady has?
- What signs & symptoms are consistent with that diagnosis?
- What are some possible causes?

- Do you see any potential DRPs?

Hypothyroidism - Goals of therapy

- Normalize TSH, fT4, fT3 levels
- Eliminate symptoms
- Avoid over-supplementation

Symptoms of Hypothyroidism



Thyroid replacement options

- Synthetic L-thyroxine (T4) (Synthroid, Eltroxin, Gen-levothyroxine, Soloxine, Euthyrox, NV-Thyro, Levo-T)
- Liothyronine (T3) (Cytomel)
- Thyroid hormone extract (Thyroid USP)
- T4/T3 Combinations (Thyrolar, Liotrix) - N/A in Canada

Therapeutic principles

- Initiating therapy
  - Use L-thyroxine monotherapy (JAMA 2003;290:2952-8)
    - T4+T3 replacement not superior to T4 alone on body weight, lipids, symptoms, cognition, QOL
  - Initial dosing:
    - Young adults: 75 mcg/d
    - Elderly: 50 mcg/d
    - CAD: 12.5-25 mcg/d & monitor for angina
- Better absorption when taken @HS (Clinical Endocrinology 2007;66:43–48; Arch Intern Med. 2010;170(22):1996-2003)
- Better absorption when taken on empty stomach (J Clin Endocrinol Metab 2009;94:3905–3912)

Therapeutic principles

- Titrating / monitoring therapy
  - Re-measure TSH (+/- fT3/fT4) 3-6 weeks after dose change
  - Once on appropriate dose, measure TSH annually
  - Adjust doses in 25 mcg/d increments
  - Mean required dose 1.5 mcg/kg/d (100-125 mcg/d)
  - No clinical advantage (QOL, Sx, cognition) to aiming for low half (<2) of normal TSH range vs. upper end (>2) (Walsh et al. J Clin Endocrinol Metab 2006:91: 2624 –2630)
  - No routine role for T3, combinations

Drug-related causes of hypothyroidism

Absorption interference
calcium, iron, aluminum supplements, sucralfate, cholestyramine, PPI?, coffee?

Inhibited T3/T4 production
iodine, amiodarone, lithium, PTU, methimazole (MMI), I131, aminoglutethimide

Inhibited TSH release
dopamine, dobutamine, octreotide (>100 mcg/d), prednisone (>20mg/d), metformin? carbamazepine?

Thyroiditis
interferon, interleukin-2, amiodarone, sunitinib

Inhibited T3-->T4 conversion
propranolol, atenolol, alprenolol, PTU, dexamethasone, prednisone, iopanoic acid, amiodarone

Displacement from TBG
estrogen, tamoxifen, raloxifene, carbamazepine, phenytoin

Unknown
valproic acid, phenobarbital, rifampin

adapted from
B.R. Haugen BR. Best Pract & Research Clin Endocrinol & Metab 2009;23:793–800

L-thyroxine: adverse effects

- Hyperthyroidism
  - Low TSH
  - Signs & Symptoms
    - Atrial fibrillation
  - Osteoporosis
    - TSH <0.1 → 3.6 x ↑ in hip fracture risk & 4.5 x ↑ in vertebral fracture risk vs. normal TSH in women >65 y/o. (Bauer et al. Ann Intern Med 2001;134:561-568; Arch Intern Med 2010;170:1876-83)

Case

- ID&CC: 76 y/o M admitted to hospital 4SEP for FTT.
- HPI: weakness, lethargy, anhedonia
- PMH: seizure disorder, schizophrenia, asthma/COPD, HTN, PVD, DM2, Graves' disease (I131 thyroidectomy)
- MPTA: several, including phenytoin 300mg HS, levothyroxine 150 mcg/d.
- Course in hospital: TSH 4SEP: 43. PHT 4SEP: 119 mg/dL (N 40-80).
  - L-thyroxine dose reduced to 50mg/d on day of admission.
- You see the patient on your unit on 18SEP. Still weak, lethargic. Na 131.

WHAT DO YOU DO?

Case

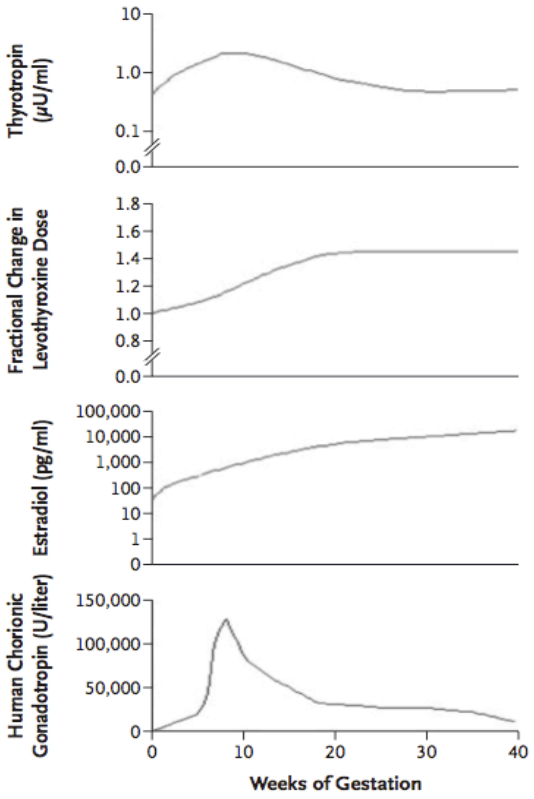
- 27 y/o F attends your family practice clinic today.
- CC: None. Regular followup visit. She advises that she is trying to become pregnant and wonders if there are any implications because of her thyroid condition.
- PMH: primary hypothyroidism
- Medications on profile:
  - levothyroxine 37.5 mcg.
- Normal labs as of 1 month ago.

Primary hypothyroidism & Pregnancy

- Epidemiology
  - 1-2% of pregnant women receive L-thyroxine for primary hypothyroidism
  - 2.5% of pregnant women have TSH >6, 10% of these have symptomatic hypothyroidism
- Pathophysiology
  - T4 & T3 fall normally throughout pregnancy
  - Estrogen → ↑TBG → ↓fT4 & fT3
- Concern: impaired fetal cognitive development and ↑ fetal mortality

Bungard & Hurlburt CMAJ 2007;176: 1077-8
Toft A. NEJM 2004;351:292-4
Alexander EK et al. NEJM 2004;351:241-9

- N=22 pregnancies in hypothyroid women
- q2 weekly lab tests
- 17 required increased thyroxine dose to maintain target TSH
- Mean 47% ↑ thyroxine dose needed
- First needed ~8 weeks



Alexander EK et al. NEJM 2004;351:241-9

Primary hypothyroidism & Pregnancy

- Counsel women with primary hypothyroidism before pregnancy
- Options:
  - Increase L-thyroxine dose by 25-50 mcg/d immediately
  - Take an extra L-thyroxine dose twice weekly beginning immediately
- Measure TSH & T4 as soon as pregnancy detected
- Measure TSH & T4 every 6-8 weeks throughout pregnancy
- Target TSH: <2.5 in 1st trimester, <3 in 2nd trimester, <5 in 3rd trimester [J Clin Endocrin Metab 2007;92:S1–S47]

Bungard & Hurlburt CMAJ 2007;176: 1077-8
Toft A. NEJM 2004;351:292-4
Alexander EK et al. NEJM 2004;351:241-9

Increase by 2 or 3 tablets per week when first pregnant?

- n=48 newly pregnant hypothyroid patients. Unblinded RCT.
- Group A: 2 extra doses/week. Group B: 3 extra doses/ week.
- Results
  - 94% kept their **TSH <5**.
  - **TSH <0.5**: Group A: 32%. Group B: 65% ($p<0.05$)
  - Risk factors for 3 being too much: prepregnancy TSH<1.5, prepregnancy dose >100mcg
  - q4 weekly TSH monitoring identified 92% of abnormal values

Yassa L, et al. J Clin Endocrinol Metab 2010;95: 3234–3241.