Systemic Management of Graves’ Disease

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Graves’ Disease:
Endocrinopathy or Ophthalmopathy?

Robert James Graves, M.D., FRCS
(1796 - 1853)

• Eminent Irish Surgeon
• President of the Royal College of Physicians of Ireland
• Fellow of the Royal Society of London
• Founder of the Dublin Journal of Medical Science
• The uncredited inventor of the second hand on watches.

• No financial disclosures.
**Graves’ Endocrinopathy**

- Most common cause of hyperthyroidism
- Affects 2% of female population
- Female : male – 5-10:1
- 25-30% of patients with endocrinopathy develop ophthalmopathy (thyroid eye disease)

**Thyroid Eye Disease (TED)**

- Graves’ ophthalmopathy (TED) is the most common cause of unilateral or bilateral proptosis
- 6X more common in women than in men
- Associated with hyperthyroidism (90%), euthyroidism (6%), hypothyroidism (4%)
- Associated with severe psychosocial stress
- Associated with elevated TSH-R stimulating auto antibodies (TRAb)

**Clinical Features of TED**

- Eyelid retraction - most common
- Lid lag
- Conjunctival injection, chemosis
- Proptosis
- Restrictive extraocular myopathy-strabismus
- Optic neuropathy
**Treatment of Graves’ Endocrinopathy**

- Antithyroid drugs
- Steroids
- Biologics
- RAI
- Surgery

**Antithyroid Drugs**

- **Thionamides** - introduced in the 1940s
  - Methimazole - Tapazole (USA)
  - Propylthiouracil (USA) - ↑ risk of liver failure
  - Carimazole - pro drug of MMI (UK)

**Mechanism of Action of Thionamides**

- Inhibit thyroid hormone synthesis by interfering with thyroid peroxidase mediated iodination of tyrosine residues in thyroglobulin
- PTU blocks conversion of T4 → T3
- Possible immune suppression with ↓ TSHRAb, IL2, IL 6
- ↓ HLA class II expression
### Characteristic

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Methimazole</th>
<th>Propylthiouracil</th>
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<tbody>
<tr>
<td>Met during liver ds</td>
<td>Decreased</td>
<td>Normal</td>
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<tr>
<td>Met during renal ds</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>Transplacental pass</td>
<td>Low</td>
<td>Even lower</td>
</tr>
<tr>
<td>Levels in breast milk</td>
<td>Low</td>
<td>Even lower</td>
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### Indications for Use of Thionamides

- To achieve a euthyroid state
- Pre intervention control (I\(^{131}\), surgery)
- Treatment of choice in pregnancy, childhood, adolescence, presence of ophthalmopathy
  - I\(^{131}\) exacerbates eye disease, requires steroid cover
Methodologies for Administration

- Dose titration
- Block and replace
  - ATD and Levothyroxine replacement
- Treatment duration - 14-18 months
- Recurrence rate - 50-60% within 3-6 months of discontinuing ATD
- May require long term low dose tx

Factors Associated with Relapse

- Severe hyperthyroidism
- High serum T3/T4 ratio
- High TSHRAb levels initially or at end of therapy
- Young age
- Male sex
- Smoking
- Presence of ophthalmopathy

Factors Associated with Relapse

- Family history of autoimmune disease
- Certain genetic markers
- Large initial goiter
- Increasing goiter size during tx
- Thyroid nodularity, hypoechogenicity by imaging
- High intrathyroidal blood flow at end of ATD tx
- Long delay from start of symptoms to initiation of tx
- Problems in coping with daily life

Side Effects of Thionamides

- Incidence 5%
- MMI dose related, PTU less so
- Ok to switch meds, 50% cross over
- Urticaria, pruritis, arthralgia, fever-rx antihistamine
- Gastrointestinal complaints, abnormalities of taste and smell
- Arthritis
- Transient granulocytopenia
Serious Side Effects

• Agranulocytosis - 0.35%
• Equal frequency MMI-PTU
• Risk of pseudomonas aeruginosa sepsis
• Hepatotoxicity - 0.1-0.2%
• Vasculitis (PTU>MMI) - lupus like
• Hypoprothrombinemia
• Hypoglycemia
• Pancreatitis

• MMI somewhat better side effect profile than PTU

β-Adrenergic Antagonist Drugs

• Ameliorate symptoms - sweating, anxiety, tremor, palpitation, tachycardia
• Mildly inhibits the conversion of T4 to T3
• Avoid in patients with COPD

• Propranolol

Inorganic Iodide

• Decreases T4 and T3 synthesis by inhibiting iodide oxidation and organification (Wolff-Chaikoff effect).
• Blocks the release of T4 and T3 by inhibiting thyroglobulin proteolysis.
• Lugol’s solution (8 mg iodide per drop)
• Saturated solution of potassium iodide (SSKI 50 mg iodide per drop)
• Dose: 24-50 mg/day

Glucocorticoids

• Blocks the conversion of T4 to T3 in a similar fashion to beta-blockers
• Use only in patients with ophthalmopathy due to side effects
Supplementary Agents

- Oral cholecystographic agents (e.g., sodium iopanoate, sodium ipodate) inhibit T4-deiodinase activity. Acutely lower serum T3 levels.
- Potassium perchlorate is a competitive inhibitor of iodide transport.
- Lithium acts by inhibiting T4 and T3 release from the thyroid. Dose - 900 mg q d

Novel Biologics

- Rituximab - more later
- anti-B-cell maturation factor
- anti-B-cell maturation antigen receptor (anti-BAFF)
- anti-B-cell maturation antigen (anti-BCMA)
- blockade of the CD40-CD154 (CD40-ligand)
- abatacept (CTLA-4/Ig);

Radioactive Iodine (RAI)

- Introduced in the 1940s (MIT, Berkeley)
- $^{131}$I concentrated, oxidized, organified by follicular thyroid cells
- Ionizing effect of $\beta$ particles (path length of 1 to 2 mm) destroys thyroid follicular cells and promotes vascular occlusion
- Induces hypothyroidism
**I\textsuperscript{131} Dosing**

- No consensus – induce hypothyroidism or retreat
- Incidence of hypothyroidism independent of dose: 2-3% annually
- Dose (mCi) = 80-200 microCi I\textsuperscript{131}/g thyroid x estimated thyroid gland weight (g)/24 hour radioiodine uptake
- Typical activities - 5 to 15 mCi I\textsuperscript{131}
- Corresponds to 185-555 MBq = absorbed radiation dose of 50 to 100 Gy.

**Becquerel**

- The becquerel (Bq) is the SI derived unit of radioactivity. One Bq is defined as the activity of a quantity of radioactive material in which one nucleus decays per second. The Bq unit is therefore equivalent to s\(^{-1}\). The becquerel is named for Henri Becquerel, who shared a Nobel Prize with Pierre and Marie Curie for their work in discovering radioactivity.

**Scan of thyroid 24 h after intake of I\textsuperscript{131}**

**I\textsuperscript{131} Influence on Thyroid Function**

- 50-70% euthyroid within 6-8 weeks
- 10 to 15 mCi (370–555 MBq) range, 80% to 90% of patients become euthyroid or hypothyroid after one dose of I\textsuperscript{131}.
- 10-20% require a second dose
Carcinogenicity

- Avoid use of $^{131}$I in children and adolescents
- Avoid use in pregnant or breastfeeding women

Factors that Increase Risk of TED

- Smoking
- High levels of pretreatment serum T3 (twice the upper limit of normal)
- A high TSH-receptor antibody titer

RAI and TED

- RAI is associated with increased risk of ophthalmopathy compared with antithyroid drugs.
- The risk of developing new or worsening ophthalmopathy is ~20% after radioiodine and ~5% after antithyroid drugs.
- Post radioiodine hypothyroidism ↑ risk of TED

- Post radioiodine hypothyroidism should be treated promptly.
- Patients with mild pre-existing ophthalmopathy, should be pretreated with prednisone to prevent progression.
- Routine use of prophylactic steroids in all RAI pts is not indicated at present but should be considered in pts at higher risk of TED (e.g. smokers).
Surgery

- Children, adolescents, pregnant women
- Large goiters (pressure symptoms, cosmesis)
- Suspicion of thyroid malignancy
- Graves’ ophthalmopathy especially those not responsive to ATD.

Complications of Thyroidectomy

- Permanent damage to the recurrent laryngeal nerve and hypoparathyroidism - (1-2% up to 5-10%)
- Transient hypocalcemia, bleeding, wound infections, keloids.
- Hypothyroidism (12-80% during the first year and at a rate of 1-3% annually)
- Subtotal thyroidectomy associated with recurrent hyperthyroidism in 5-15%
Choices?

• Preference for ATD, $^{131}$I or surgery should be discussed with patient and endocrinologist on an individualized level.

• Stop smoking!

References


• Ponto, K, The Tale of Radioiodine and Graves’ Orbitopathy, Thyroid, 20(7), 2010
