Antithyroid Drugs

A 30 years old female presented with Lack of energy, weight gain, her voice became husky recently she also complains of intolerance to cold. On examination she was found with delayed ankle jerk and dry skin.
What is the likely diagnosis?

Thyroid Diseases:

- Hypothyroidism:
  - Cretinism (in children)
  - Myxedema (in adult)
- Hyperthyroidism:
  - Thyrotoxicosis
  - Grave's disease.

HYPOTHYROIDISM	HYPERTHYROIDISM
• Hoarseness of voice • Weight gain • Cold intolerance • Dry skin and hair • Constipation	• Palpitation • Weight loss • Heat intolerance • Dry skin and hair • Diarrhoea

Hyperthyroidism:

- Occur due to increased activity of thyroid hormones or excessive intake.
  - S/S: wt. lose, tachycardia, heat-intolerance.
- Graves disease: is an autoimmune disorder due to the presence of autoantibodies.
  - S/S: Enlargement of thyroid gland, hot flush.
- **Treatment: Thioamides, radioactive iodine, thyroidectomy.**

Hypothyroidism:

- Due to decrease in T4 and T3
  - S/S: wt. gain, cold intolerance, deep hoarse voice. Delayed ankle reflex.
- Myxedema: Feature of hypothyroidism where accumulation of mucopolysaccharide in the intercellular spaces of muscle and skin.
- **Treatment: Levothyroxine, Liothyronine, Liotrix**

Subclinical Hypothyroidism:

- In subclinical hypothyroidism there is-
    - Normal serum free T3 and free T4
    - Low serum TSH
- 5% patient progress to frank hypothyroidism
- Increase risk of atrial fibrillation, stroke and osteoporosis
- Treatment should be considered when the TSH level is less than 0.1mU/L, specially in patients aged over 60
- Patients need to monitor 6 monthly

Drugs used in Hypothyroidism:

- Levothyroxine (T4)
- Liothyronine (T3)
- Liotrix (mixture of T4 and T3)

Kinetics of Drugs:

Levothyroxine (T4):

- Given orally, bioavailability is 80%
- Low cost, high stability
- Less antigenic.
- Long half life- 7 days (once daily dose)
- Since T4 is converted to T3, administration of Levothyroxine (T4) can replace both the hormones (T4, T3).
- Is the drug of choice in hypothyroidism

Liothyronine (T3):

- Given orally, bioavailability is 95%
- 3-4 times more potent than levothyroxine
- Expensive, difficulty to monitor plasma level
- Short half life (not used for routine replacement)
- Its greater hormonal activity increases the risk of cardiotoxicity

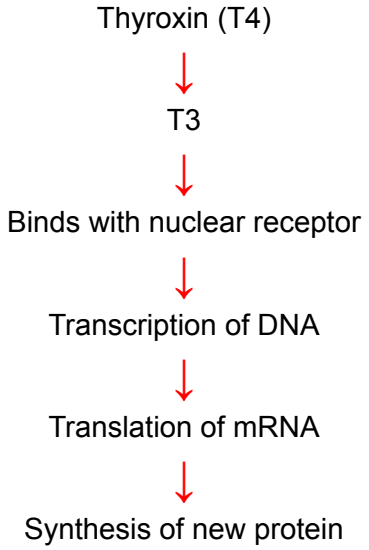
Liotrix (T4 and T3):

- Given orally
- Is a mixture of thyroxine and levothyroxine
- Expensive

Disadvantage:

- Since administration of T3 is not preferred so combination is not used.
- Can cause Hyperthyroidism and cardiotoxicity.

Mechanism of action



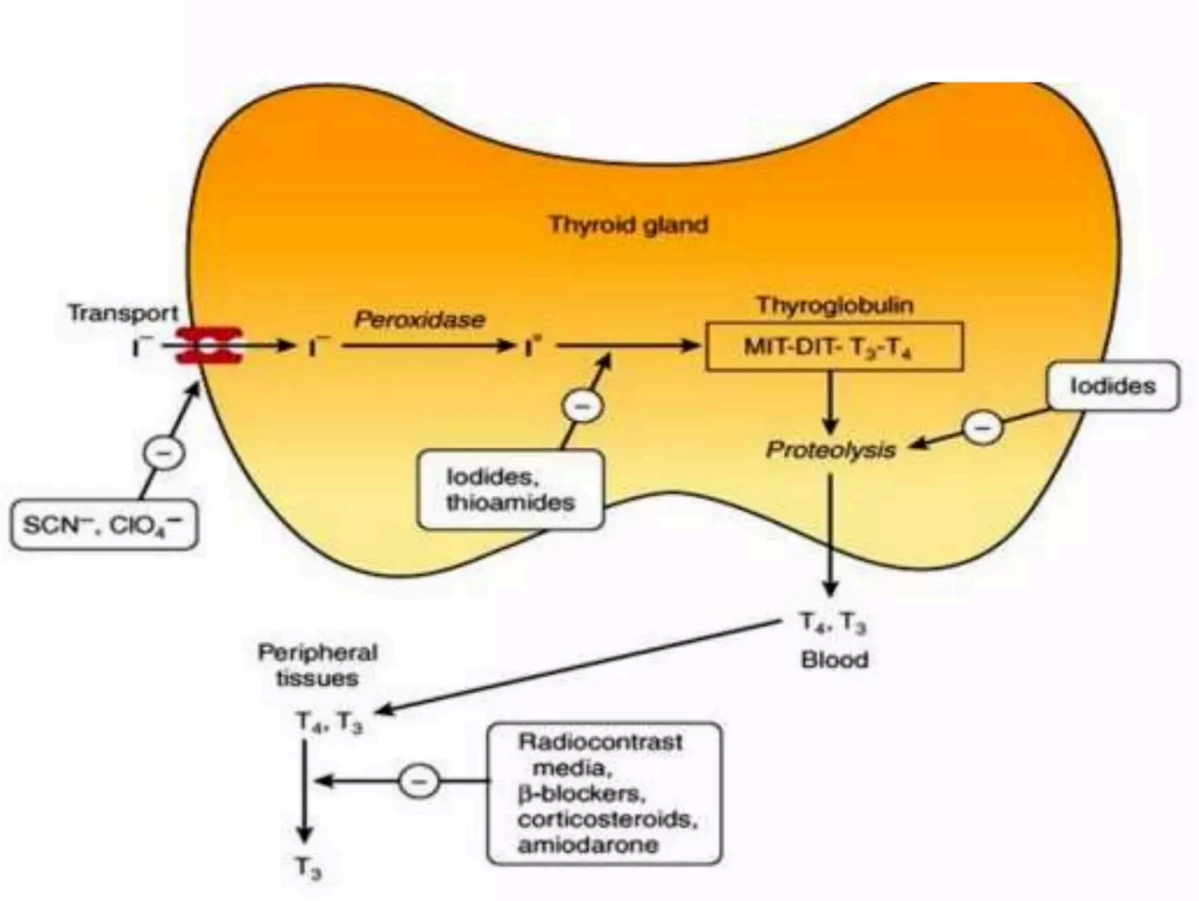
Drugs used in Hyperthyroidism:

- Thioamides
  - Propylthiouracil
  - Carbimazole
  - Methimazole
- Iodides
  - Potassium iodide
  - Sodium iodide
- Radioactive iodine

Thioamides:

- **Propylthiouracil (PTU)**
  - Is the prototype of the group, labelled as goitrogens.
  - Preferred in pregnancy, because it does not cross the placenta
  - Not secreted in breast milk
  - Inhibiting thyroid hormone synthesis but has no effect on already formed thyroxine.
- **Methyl thiouracil**
  - Have equal potency to PTU
  - Exert allergic manifestation
- **Carbimazole**
  - As effective as PTU, Can cross placenta
- **Methimazole**
  - Is an active metabolite of Carbimazole
  - Chemically similar to PTU
  - 10 times more potent than PTU.
  - Duration of action is 30-40 hours.
  - It is teratogenic and less amount secreted in breast milk

Mechanism of antithyroid drug



Mechanism of Thioamides:

- Prevent thyroid hormone synthesis by -
    - Inhibiting thyroid peroxidase enzyme.
    - Blocking iodine organification.
    - Blocking coupling of the iodotyrosine.
- Inhibit the peripheral conversion of T4 to T3

Adverse effects of Thioamides:

- Allergic action - Urticaria, Maculopapular rash (most common)
- Nausea, headache, joint pain, loss of hair
- Goitrogenic action
- Agranulocytosis (rare)

Contraindication:

- Use should be minimised in pregnancy (It crosses placenta can cause foetal goitre)
- Should not be used in Lactating mother.

Comparison

Propylthiouracil	Carbimazole
Less potent	More potent
High plasma protein binding	Remain in free form
Less transported across placenta barrier and milk	Can cross placental barrier
Safe in pregnancy and in nursing mother	Not recommended
Short half life (1-2 hour)	Long half life (6-10 hours)
Frequent dosing required	Single dose needed
Also inhibit conversion of T4 to T3	Does not have this effect

Kinetics of iodide:

- Well absorbed from the intestine.
- Selectively taken up and concentrated by the thyroid gland (more in hyperthyroidism and less in hypothyroidism)
- Effects are visible within 24 hours
- Rapidly excreted by the kidney
- It is no longer used in long term therapy

Mechanism of iodide:

- Small amount of iodine (75-100 ng/day) is required for hormone synthesis but high concentration (50mg/day) of iodine results in auto inhibition.
- Blocks uptake of iodide, inhibits synthesis and release of thyroid hormone.
- Reduces vascularity of thyroid gland.

Adjunct to Antithyroid therapy:

Hyperthyroidism resembles sympathetic over activity.

- **Propranolol** - will control tachycardia, hypertension, atrial fibrillation, inhibit conversion of T4 to T3.
- **Diltiazem** - control tachycardia where Propranolol is contraindicated.
- **Barbiturate -** accelerate T4 breakdown (since it is enzyme inducer).

Thyroid disease and Pregnancy

- Pregnancy with hypothyroid:
    - The dose of Levothyroxine should be adequate, because development of foetal brain depends on maternal thyroxine
- Pregnancy with hyperthyroid:
    - If thyrotoxicosis develops, Propylthiouracil is used and an elective subtotal thyroidectomy is performed

ATD regimen for Hyperthyroidism

- **Titration method:**
    - Starting with Methimazole (15-30 mg/day), daily dose is tapered down to the lowest effective dose. Thyroid function assessment 4 monthly until treatment is stopped after 18-24 months.
- **Block and replacement method:**
    - Use of persistently high dose of antithyroid drugs in association with Levothyroxine replacement to avoid hypothyroidism; treatment lasts 6 months Contraindicated in pregnancy.