Thyroid and Anti-Thyroid Drugs

Normal thyroid gland secretes:

**1-Thyroid hormones:**

● Tri-iodothyronine (T3), contain 59% of iodine

● Tetraiodothyronine (T4, thyroxine), 65% iodine

**To :**

■ Normalize growth and development

■ Control body temperature

■ Energy levels

**2-Calcitonin, regulate Ca metabolism.**

Effects of Thyroid Hormones

● Responsible for optimal growth, development, function and maintenance of all body tissues

● Critical for nervous, skeletal and reproductive tissues

● Its effects depend on pituitary synthesis + potentiation of the secretion and action of growth hormone

● Inadequate secretion in early life: irreversible mental tetardation (cretinisim) and dwarfism or congenital cretinism

● Effect on growth and calorigenesis

● Influence metabolism of drugs, carbohydrates, fat, proteins and vitamins

● The secretion and degradation of rates of all other hormones as catecholamines, cortisol, estrogen, testosterone and insulin are affected by thyroid status

● Many of the manifestation of thyroid hyperactivity resemble sympathetic nervous system over activity due to oversensitivity of β receptors or increase in their number , there may also be increase in the production of catecholamines

Manifestation of hyperthyroidism:

● Nervousness, irritability, anxiety, restlessness

● Tremors, palpitation

● Weight loss

● Increased perspiration

● Heat intolerance

● Diarrhea

● Shorth breath

● Thinning of skin and brittle hair

●Weakness

● *In women:* irregular menstrual periods or stop having their periods altogether, this can be associated with infertility

● *In men:* they may develop enlarged or tender breasts or erectile dysfunction which resolves when hyperthyroidism is treated

Manifestation of hypothyroidism (underactive thyroid):

● Fatigue and lack of energy

● Weight gain

● Dry, coarse and cold skin

● Constipation

● Slowed thinking and difficulty in concentrating

● Bradycardia

● Depression

● Dry and coarse hair

●Heavy menses

Causes of Hypothyroidism

■ Drugs (metabolism)

■Autoimmune destruction

■ Blocked hormone formation

■ Impaired synthesis of T4

■ Destruction or removal of the gland

■ Iodine deficiency

■ Receptor blocking antibody

■ Pituitary or hypothalamic disease

Biosynthesis of thyroid hormones



● Iodide is taken up by the thyroid gland that convert it into active thyroid hormone by enzymatic reactions:

1- Transport of iodide into the thyroid gland by Na/iodide symporter

2-At the apical cell membrane, iodide is oxidized by thyroidal peroxidase to iodine, which rapidly iodinates tyrosine residue within the thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT)

2 molecules of DIT + thyroglobulin = L-thyroxin (T4)

1 moleclue of MIT + DIT = T3

This process called **iodide organification/ iodination**

● These hormones are released by exocytosis and proteolysis of thyroglobulin

● Only 0.04% of total T4 and 0.4% of T3 exist in the free form

● T3 and T4 in plasma are reversibly bound to thyroxin-binding globulin (TBG)

● The ratio of T4 to T3 within thyroglobulin is 5:1, so most of the hormone released is thyroxin and most of T3 in the circulation is derived from metabolism of T4

 Peripheral Metabolism

● The primary pathway for the peripheral metabolism of thyroxin is de-iodination.

● Monodeiodination of the outer ring of T4:T3, which is 3-4 times more potent than T4

● Deiodination of the inner ring, producing reverse T3, which is metabolically inactive

● Drugs like ipodate, amiodarone, β-blockers, corticosteroids and severe illness or starvation inhibit 5-deiodinase, resulting in low T3 and high T4

Thyroid-Pituitary Relationships

● Hypothalamus cells secrete thyroid releasing hormone (TRH), that stimulate pituitary gland to release thyroid secreting (TSH).

● TSH stimulates adenyly cyclase-mediated mechanism in the thyroid cell to the synthesis and release of T₄ and T₃.

● These thyroid hormones act in a –ve feedback fashion in the pituitary and in the hypothalamus.

● Also large doses of iodine inhibit iodide organification.

Pharmacokinetics of Thyroid Hormones

● Thyroxine is absorbed in the duodenum and ileum, altered by food and antacid.

●Oral bioavailability: T₄ → 80%, T₃ →95%

● Absorption is not affected by mild hypothyroidism or impaired in severe myxedema with ileus, so switch to IV.

● In hyperthyroidism, the metabolic CI of T₄ and T₃ are and increase the t½. The decrease opposite is true in hypothyroidism.

● Enzyme inducers increase thyroxine hormones metabolism, or hormone concentration is remained normal in euthyroid (compensatory hyper function of the thyroid).

Same compensation occurs if TGB increased by pregnancy, estrogens, or OCCs.

MOA

● T₄ and T₃ dissociate from TGB, entering the cell by active transport.

● Within the cell T₄ is converted to T₃ by deiodinase , and T₃ enters the nucleus, where T₃ binds to a specific T₃ receptor

● This leads to increase formation of RNA and subsequent protein synthesis.

● Most of the receptors are found in pituitary, liver, kidney, heart, skeletal muscle, lung and intestine.

Thyroid Preparations

Levothyroxine (T₄):

■ Synthetic levothyroxine is the preparation of choice for thyroid replacement and suppression therapy because of its stability, lack of allergenic foreign protein and long t½ (7d), so OD

**Preparations available:**

● Po: 0.025-0.3 mg tablets

● Parenteral use: 200-500 µg/ml.

Liothyronine (T₃):

● 3-4 times → potent and rapid acting than T₄ or has a shorter t½ (24hr), so not recommended for routine replacement therapy (requires multiple dosing in a day).

● Has greater risk of cardiotox, so avoided in cardiac patients.

● Po: 5-50µg tab

● Parenteral: 10 mg/ml

Comparison of T₄ to T₃

► T₄ production is > T₃

► T₄ is converted to T₃ in periphery

► T₃ is > potent than T₄

►T₃ act faster than T₄

► T₃ enters cell easily than T₄

►T₃ binds to Rs in nucleus.

Anti-Thyroid Agents

● They interfere with the production of thyroid hormones.

● They modify the tissue response to thyroid hormones or glandular destruction with radiation or surgery.

## Drugs:

□ Thioamides

□ Iodides

□ Radioactive Iodine

□ Iodinated Contrast Media

□ Adrenoceptor-Blocking Agents

□ Anion Inhibitiors

Thioamides

● Methimazole and propylthiouracil (PTU) are major drugs for treatment of thyrotoxicosis

● In UK, Carbimazole is converted to Methimazole, widely used

● Methimazole is 10 times more potent than PTU

Pharmacokinetic comparison between Methimazole and PTU:

|  |  |  |
| --- | --- | --- |
|  | PTU | Methimazole |
| Absorption | Rapid – incomplete | At variable rates- complete |
| Volume of Distribution | Approximates body waters | similar |
| Protein Binding | More | less |
| Accumulation | In thyroid | similar |
| Excretion | Kidneys as inactive Glucuronide in 24hrs | Slow , 60-70% of drug is recovered in urine in 48hrs |

PK comparison between PTU & Methimazole

|  |  |  |
| --- | --- | --- |
| Methimazole | PTU |   |
| 6 hrs | 1.5 hrs | Half life |
| Single dose in 24 hrs | Every 6-8 hrs | Administration |
| 30 mg exert anti thyroid effect for longer than 24 hrs | 100 mg inhibit iodine organification for 7 hrs | Duration of activity |
| Cross placenta & concentrated by fetal thyroid | Highly pt bound, cross placenta less readily | pregnancy |
| secreted | ˂secreted in breast milk | Nursing mothers |

Pharmacodinamics

● They prevent hormone synthesis by inhibiting the thyroid peroxidase -catalyzed reactions to block iodine organification

● They block coupling of iodotyrosine of T4 to T3.

● The onset of these agents is slow/delayed, because they effect the synthesis (rather than the release) of hormones, often requiring 3-4 weeks before stores of T4 are depleated.

Toxicity

● Side effects occur in 3-12 % of treated patients.

● Maculopapular pruritic rash & fever

● Urticarial rash , vasculitis, lymphadenopathy &hypothrombinemia.

● Altered sense of taste / smell(methimazole)

● Hepatitis(PTU)

● Cholestatic jaundice (more e methimazole)

● Granulocytosis, most dangerous, unfrequent\fatal especially in elderly & high dose.

Iodides

● Iodides were the major antithyroid agints, today they are rarely used alone.

MOA:

● Inhibit organification & hormone release thru inhibition of thyroglobulin proteolysis (e dose of ˃6 mg /day)

● Rapid improvement in thyrotoxic symptoms occure within 2-7 days (very valuable in thyroid storm) .

● Iodide decrease the vascularity & size of a hyperplastic gland, (valuable as preoperative preparation for surgery)

● Well and rapid absorbed from intestine.

● Rapidly taken by thyroid gland and concentrated there.

● Iodide should be initiated after onset of thioamide & avoided e radioactive iodine.

● Because an increase in intraglandular stores of iodine, may delay the onset of thioamide therapy / prevent use of radio active iodine therapy for several weeks.

● Iodide should not be used alone , because the gland will escape from the iodide block in 2-8 weeks & its withdrawal may produce sever exacerbation of thyrotoxicosis in an iodine- enriched gland.

● Should not be used in pregnancy , because they cross placenta & can cause fetal goiter.

Toxicity

● Iodism: acneiform rash, swollen salivery gland, mucous membrane ulcerations, rhinorrhea, fever, metallic taste, bleeding disorder & rarely anaphylactic rxs.

Radioactive Iodine

● 131| isotope used for treatment of thyrotoxicosis.

● Administrated orally in solution as Na 131|, rapidly absorbed, concentrated by the thyroid& incorporated into storage follicles.

MOA:

● Emission of β rays e an effective t1/2 of 5 days causes destruction of the thyroid parenchyma within a few weeks, necrosis & follicular disruption.

**Advantages of Radioiodine:**

►Easy administration

►Effectiveness

►Low expense

►Absence of pain

►Should not be administered to pregnant women/nursing mothers , because it cross the placenta , destroy the fetal thyroid gland, genetic damage, leukemia/carcinogenic & is excreted in breast milk.

►Given only for patient ˃ 40 years

Idonated Contrast Media

● Ipodate, iopanoic ; po

● Diatrizoate po & iohexol (po/IV), are  valuable in treatment of  hyperthyroidism

● Rapidly inhibit the conversion of T4 to T3

● Provide useful adjunct in the treatment of thyroid storm & offer valuable alternatives when iodides/thioamides are Cl

Adrenoceptor-Blocking Agents

● Symptoms of thyrotoxicosis mimic sympathetic over stimulation .

● β blockers without intrinsic activity (propranolol,atenolol) are effective therapeutic adjunct in the management of thyrotoxicosis.

● β blockers cause clinical improvement of hyperthyroid symptoms.

Anion Inhibitors

● Monovalent anion:perchlorate (ClO4¯), pertechnetate(TCO4¯) & thiocyanate(SCN¯) can block uptake of iodide by the gland thru competitive inhibition of the iodide transport mechanism.

● For this purpose large doses of the drug are required.

● Rarely used because they cause aplastic anemia.

Hypothyroidism

● Is a syndrome resulting from deficiency of thyroid hormone and is manifested by reversible slowing down of all body functions.

● In infants/children: retardation of growth and development that result in dwarfism and irreversible mental retardation.

● Can occur with or without thyroid enlargement (goiter).

● *Lab diagnosis:* ↓ free thyroxine ↑ serum TSH (Thyroid Stimulating Hormone).

● The most common cause of hypothyroidism is Hashimoto's thyroiditis, an immunologic disorder in genetically predisposed individuals.

 Management of Hypothyroidism

● Replacement therapy: levothyroxine.

● Infants and children require > T4/ kg of body weight than adults.

● Start with low dose in long-standing hypothyroidism, in older patients, and in patients with cardiac disease.

● Administered as an oral drug, on an empty stomach (30 minutes before meals or 1 hour after meals).

 Toxicity of T4:

● In children: restlessness, insomnia, and accelerated bone maturation and growth.

● In adults: increased nervousness, heat intolerance, episodes of palpitations and tachycardia, weight loss.

● Chronic over treatment with T4, especially in elderly patients, can increase the risk of atrial fibrillation and osteoporosis.

 Myxedema Coma:

► It is an end state of untreated hypothyroidism, requires medical emergency.

► It is associated with stupor, hypothermia, hypoventilation, hypoglycemia, shock and death.

**Treatment of Myxedema coma:**

□ Loading dose levothyroxine IV therapy (300 – 400 μg, followed by 50 – 100 μg daily).

□ IV T3 can be used but it's more cardiotoxic and more difficult to monitor.

□ IV hydrocortisone if the patient has adrenal/pituitary insufficiency

 Hypothyroidism and Pregnancy

● Hypothyroid women frequently have anovulatory cycles and are therefore, relatively infertile until restoration of euthyroid state.

 ● *Treatment:* by daily dose of thyroxine.

 ● In pregnant hypothyroid patients (20 – 30%) an increase in thyroxine is required because of elevated maternal TBG (thyroxine-binding globulin) and early development of fetal brain which depends on maternal thyroxine.

Hyperthyroidism = Thyrotoxicosis:

● Tissues are exposed to high levels of thyroid hormone.

 Grave's Disease:

■ Is the most common form of hyperthyroidism

■ It is an autoimmune disorder in which there is a genetic defect in suppressor T-lymphocytes that stimulate B-lymphocytes to synthesize Thyroid Stimulating Hormone – Receptor (TSH-R) stimulating antibodies in the thyroid gland and has the capacity to stimulate growth and biosynthetic activity of the thyroid cell

 Lab Diagnosis

● ↑ level of T3 and T4

● TSH is ↓

● Radio iodine uptake is elevated

 Management of Grave's Disease:

● Antithyroid drug therapy

● Surgical thyroidectomy

● Destruction of the gland with radioactive iodine

Anti-Thyroid Drug Therapy

● Most useful in young patients with small glands and mild disease

● Methimazole/ PTU (Propylthiouracil) is administered until the disease undergoes spontaneous remission

● Requires a long period of treatment and observation about 1 -2 years, with 50 – 70% relapse

● Start with large divided dose, then shift to maintenance single daily dose

● PTU inhibits iodine organification and conversion of T4 to T3, so it brings the levels of activated thyroid hormone down faster than methimazole does

 Thyroidectomy

● A near total thyroidectomy is the treatment of choice for patients with very large glands or multinodular goiters.

● In case of multinodular goiter and to simplify surgery (to diminish vascularity): Saturated solution of K iodide 5 drops twice a day for 2 weeks prior to surgery.

Radioactive Iodine

● 131I is the preferred treatment for most patients over 21 years of age, in a dose of 80 – 120 MicroCi/g of thyroid weight (in patients without heart disease).

● In patients with underlying heart disease/severe thyrotoxicosis/ elderly, use methimazole until patient becomes euthyroid, then stop the medication 5 – 7 days before the 131I.

● Major complication of 131I: hypothyroidism (80% of the patients).

 Adjunct Therapy:

● During acute phase β blocker is extremely helpful

● Propranolol 20 – 40 mg orally every 6 hours, will control tachycardia, hypertension, and atrial fibrillation

● If β blocker is contra-indicated, diltiazem 90 – 120 mg 3-4 times daily can control tachycardia

 Thyroid Storm (Thyrotoxic Crisis)

● Is sudden acute exacerbation of all of the symptoms of thyrotoxicosis.

● It is a life threatening syndrome.

● There is hyper-metabolism, excessive adrenergic activity, death may occur due to heart failure and shock.

Vigorous management is mandatory:

1. Propranolol 1-2 mg slowly IV, to control severe cardiovascular manifestations.

2. KI (Potassium iodide) 10 drops orally daily, or Iodinated contrast media (Na ipodate 1 g orally daily).

3. PTU 250 mg orally every 6 hours; can be given rectally.

● Hydrocortisone, 50 mg IV every 6 hours to prevent shock.

●If the above methods fail, plasmapheresis/peritoneal dialysis is done.

 Thyrotoxicosis During Pregnancy

● Definitive therapy: 131I/subtotal thyroidectomy prior to pregnancy in order to avoid an acute exacerbation of the disease during pregnancy/after delivery.

● If thyrotoxicosis develops during pregnancy:

1. Radioiodine is contraindicated.

2. In the first trimester, the patient can be prepared with minimal therapeutic dose of PTU (<300 mg/day) and

3. Subtotal thyroidectomy performed safely during the mid trimester.