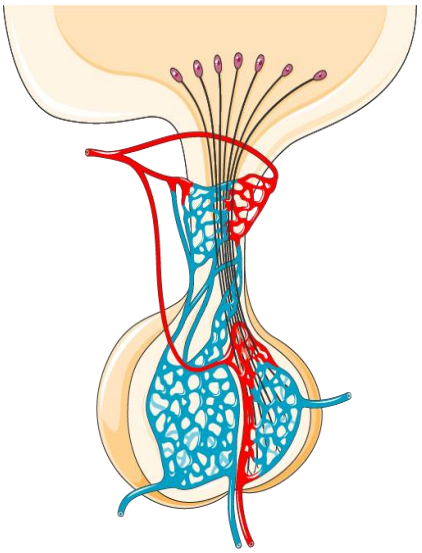
MEDICINE
KING SAUD UNIVERSITY

436 team
pharmacology



1: Drug Used In Hyperthyroidism

Objectives

1. Describe different classes of drugs used in hyperthyroidism and their mechanism of action
2. Understand their pharmacological effects, clinical uses and adverse effects.
3. Recognize treatment of special cases such as hyperthyroidism during pregnancy, Graves' disease and thyroid storm

Color index

- Extra information and further explanation
- **Important**
- **Doctors' notes**
- **Drugs names**
- **Mnemonics**

Kindly check the editing file before studying this document

Thyroid hormone

You can skip the first 4 slides if you understand physiology and biochemistry lectures

Thyroid function

- Normal amount of thyroid hormones are essential for normal growth and development by maintaining the level of energy metabolism in the tissue.
- Either too little or too much thyroid hormones will bring disorders to the body.

Important function

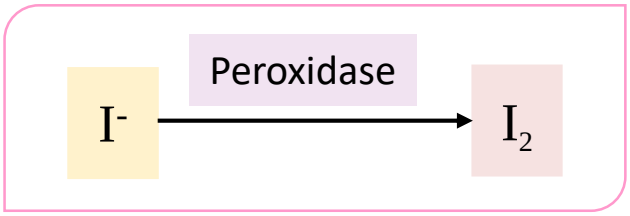
- Growth & development, especially in the embryo & brain
- Thermoregulation: increase basal metabolic rate (BMR)
- Helps maintain metabolic energy balance
- CVS: increase heart rate & cardiac output which increase oxygen demand

Iodine Importance

- Thyroid hormones are unique biological molecules in that they incorporate iodine in their structure
- Adequate iodine intake (diet, water) is required for normal thyroid hormone production
- Major sources of iodine are : iodized salt , iodated bread , dairy products , shellfish
- Minimum requirement: 75 micrograms/day

Iodine Metabolism

- Dietary iodine is absorbed in the GI tract, then taken up by the thyroid gland (or removed from the body by the kidneys)
- Iodide taken up by the thyroid gland is oxidized by peroxidase in the lumen of the follicle:



- Oxidized iodine can then be used in production of thyroid hormones

Thyroid Regulation

Thyroid regulation

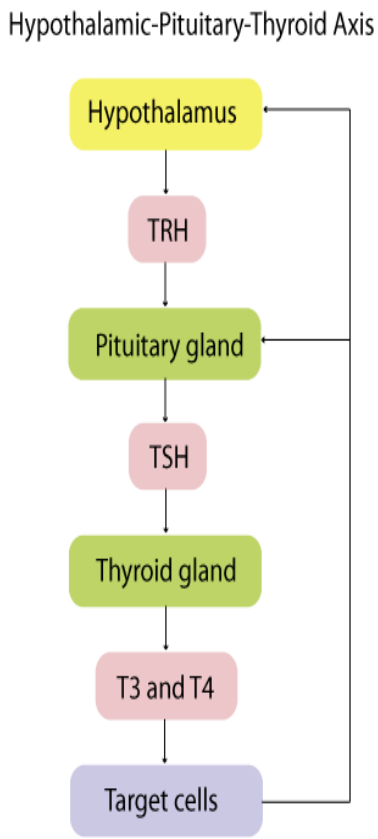
1. Hypothalamus secretes **Thyrotropin- Releasing Hormone** (TRH) which stimulates synthesis & release of thyrotropin (**Thyroid Stimulating Hormone** or TSH) by the anterior pituitary.

2. TSH then stimulates the thyroid gland to uptake iodine, synthesize & release T_4 & T_3, by increasing adenyl cyclase and cAMP.

3. T_4 & T_3 levels feedback to both hypothalamus & pituitary affecting the release of TRH & TSH.

4. **Thyroid hormones** exert negative feedback on TSH release at the level of the anterior pituitary:
   - Inhibition of **TSH synthesis receptors.**
   - Decrease in **pituitary receptor for TRH.**

- **TSH** release is influenced by hypothalamic (**TRH)**, and by thyroid hormones themselves.



The drugs work to block the receptors

Thyroid Hormones

- tetraiodothyronine (T_4; thyroxine)
- Triiodothyronine (T_3)

Thyroid Hormones Synthesis

iodine trapping: uptake of iodine by the thyroid gland → oxidation of iodine: (to its active form) thyroid peroxidase (key enzyme of the synthesis) → iodide organification: the iodination of tyrosyl groups of thyroglobulin produces : MIT and DIT → formation of T_4 and T_3 from MIT and DIT: thyroid peroxidas

Thyroid Hormones Disorders

Thyroid Hormones Disorders

THYROID NEOPLASIA

Benign enlargement or malignancies of the gland

HYPOTHYROIDISM:

Refers to disorders in which the thyroid gland secretes decreased amounts of hormones

THYROTOXICOSIS :

Is the term for all disorders with increased levels of circulating thyroid hormones

HYPERTHYROIDISM :

Refers to disorders in which the thyroid gland secretes increased amounts of hormones

THYROTOXICOSIS	HYPERTHYROIDISM
Hypermetabolic state caused by thyroid hormone excess at the tissue level	Increased thyroid hormone synthesis and secretion
Not all patients with thyrotoxicosis have hyperthyroidism . Like a problem in the secretion or excretion or drug induced	All patients with hyperthyroidism have thyrotoxicosis

Causes of thyrotoxicosis

RAUI = RadioActive Iodine Uptake
Can be used for both diagnostic and therapeutic.

With high RAIU

- Graves' disease (60-80%) most common
- Multinodular goitre (14%)
- Adenomas / carcinomas

With low RAIU

- Thyroiditis
- Iodine-induced thyrotoxicosis
- Drugs (e.g. amiodarone)
- Radiografic contrast media

Features of diseases

Features of Grave's disease (diffuse toxic goiter)

- Caused by thyroid stimulating immunoglobulins that stimulate TSH receptor , resulting in sustained thyroid over activity. it is an autoimmune disease
- Mainly in young adults aged 20 to 50
- 5 times more frequent in women
- Swelling and soft tissues of hands and feet
- Clubbing of fingers and toes
- Half of cases have **Exophthalmos** (not seen with other causes of hyperthyroidism)
- 5% have **pretibial myxedema** (thyroid dermopathy) and "square toes"

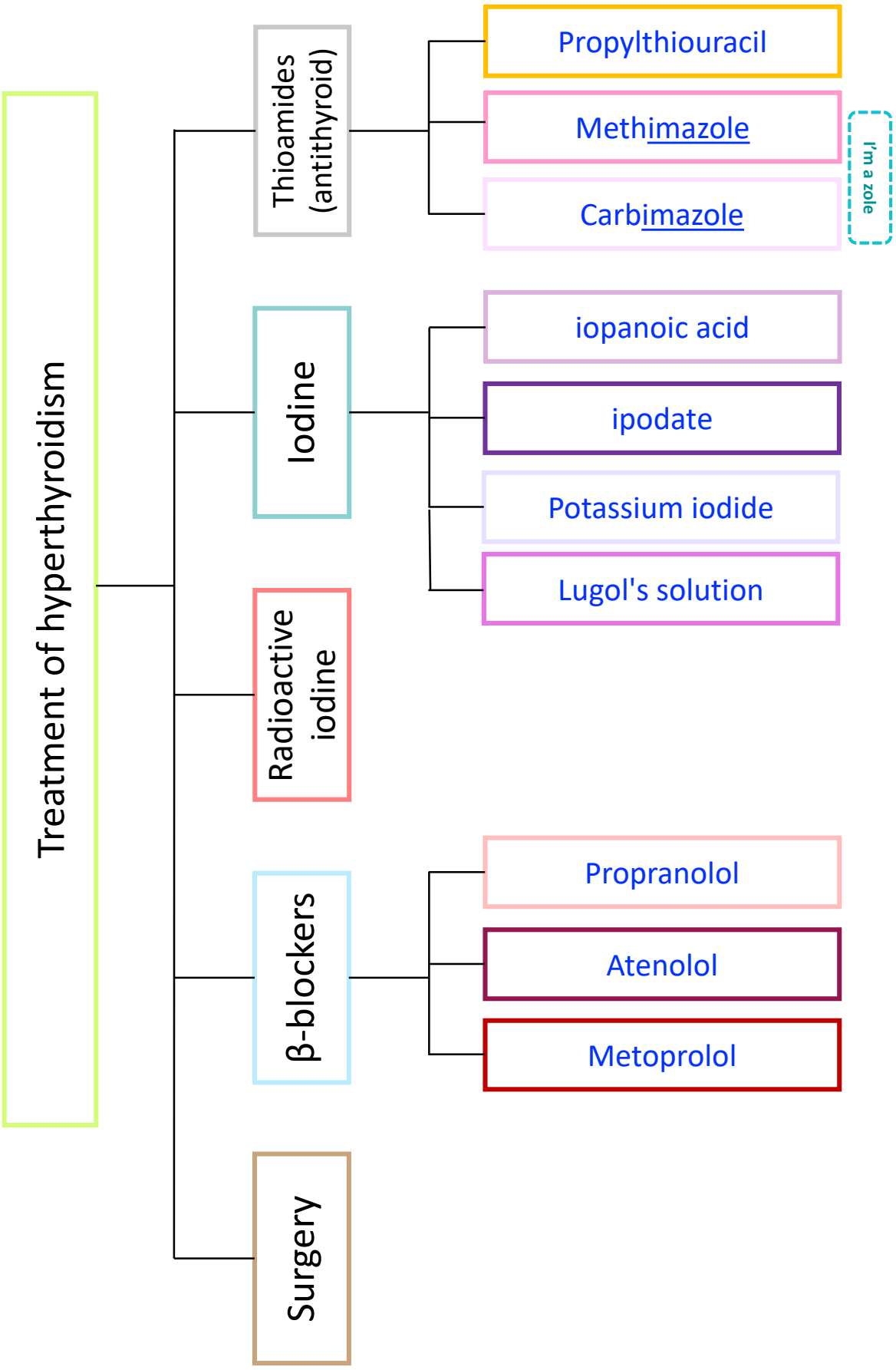
Features of Toxic Multi-nodular Goiter

- Second most common cause of hyperthyroidism
- Most cases in women in 5th to 7th decades
- Often have long standing goiter
- Symptoms usually develop slowly

Thyrotoxicosis (Just hyperthyroidism symptoms)

Symptoms	Signs
• Irritability • Dysphoria • **Heat intolerance & sweating** • **Palpitations** • Fatigue & weakness • **Weight loss** • Diarrhea	• Arrhythmia • Thyroid enlargement • Warm, moist skin • **Exophthalmus** • **Pretibial myxedema**

Overview



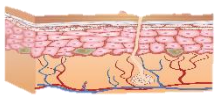
المحاضرة شرحتها لنا بروف. يلدز، اللي ركزت عليه حطيناه لكم **بالعنابي**

1-THIOAMIDES[1]

	Propylthiouracil (PTU)	Methimazole , Carbimazole (pro-drug converted to the active metabolite methimazole)
Mechanism of action	Inhibit synthesis of thyroid hormones by inhibiting the **peroxidase** enzyme that catalyzes the iodination of tyrosine residues	
	Propylthiouracil (but not methimazole) blocks the conversion of T_4 to T_3 in peripheral tissues	يعني هذا الدوا عنده طريقتين عشان يشتغل اذا جبت في الاختيارات اللي فوق او اللي تحت الاثنين صح
Absorption	Rapidly absorbed	Rapidly absorbed
Administration	Every 6-8 hours	Every 8 hours
Accumulation	in thyroid	in thyroid
Excretion	Kidneys as inactive metabolite within 24 hours Propylthiouracil, fast=Acil معناها بالتركي مستعجل أو عاجل	I'm a zole Excretion **slow**, 60-70% of drug is recovered in urine in 48 hours
Half life	1.5 hours (short) Propylthiouracil, Prop=BRB وراجع شوي كاننا نقول برب	6 hours (long) I'm a zole, I'm long
Binding protein	80-90% **(notice its very high)** Propylthiouracil = Protein binding	Most of the drug is free. more active I'm a zole, and I'm free
Pregnancy Propylthiouracil is proper drugs to be used in pregnancy & breast feeding	Doesn't cross placenta (Crossing placenta is less readily as it is highly protein bound) Recommended in pregnancy A molecule that is bound to a protein is a lot bigger than its free form→ due to its size it can't pass through the placenta or be secreted with milk	Concentrated in Thyroid & crosses placenta Not recommended in pregnancy
Breast feeding	Less secreted in breast milk (bc it's highly protein binding) Recommended	secreted in breast milk Not recommended
Uses	• The drug of choice in pregnancy • Recommended in breast feeding	The drug of choice in adults and children (more potent than PTU)

[1] It is Important to compare between them

Adverse effect of Thioamides

The Adverse Effect	Frequency	comments
 Skin reaction	4–6%	Urticarial or macular reactions (round with fluid inside)
 Arthralgia (pain in joints)	1–5%	____
 Polyarthritis	1–2%	It's any type of arthritis that involves 5 or more joints simultaneously So-called anti-thyroid arthritis
 GIT effect	1–5%	Gastric distress and nausea
 Immunoallergic hepatitis	0.1–0.5%	Propylthiouracil = urea is formed in the liver Almost exclusively in patients taking Propylthiouracil
 Agranulocytosis	0.1–0.5%	Seen in patients with Graves' disease; **occurs within 90 days of treatment** (this effect can be seen in both drugs 'Propylthiouracil + methimazole')
 **ANCA**-positive vasculitis *(Anti-neutrophil cytoplasmic antibodies)*	Rare	With propylthiouracil Paul.Anka: who is a Canadian-American singer, songwriter, and actor, became famous during the late 1950s, 1960s.
 Abnormal sense of taste or smell	Rare	With methimazole only Methimazole = Mouth Methimazole = اثمه أو ثمه بلهجة من اللهجات تعني فمه

Warnings (only in male's slides)	
Agranulocytosis: Patients on PTU or methimazole should be instructed to immediately report to their physicians any symptoms suggestive of agranulocytosis, such as fever or sore throat.	Congenital Malformations: Methimazole crosses the placental causing fetal harm, when administered in the first trimester of pregnancy

2-IODINE (Lugol's solution, potassium iodide)

(Two types): 1- **Organic** iodides as : iopanoic acid or ipodate

ننتبه للأسماء 2- Potassium iodide or Lugol's solution

M.O.A	• Inhibit thyroid hormone synthesis and release • Block the peripheral conversion of T_4 to T_3 • The effect is not sustained (produce a temporary remission of symptoms , which means we don't use this treatment for long time)
indication	• Prior to thyroid surgery (thyroidectomy) to decrease vascularity & size of the gland Iodine : before surgery is done. • Following radio active iodine therapy • Thyrotoxicosis
C.I	❖ Should not be used as a single therapy ❖ Should not be used in pregnancy ❖ May produce iodism (Rare, as iodine is not much used now)
ADRs	Iodism Symptoms: toxic dose of iodide (skin rash , hypersalivation, oral ulcers, metallic taste, bad breath). There is an idiot rock star who is always rash, and he likes metallic rock. Every time he stand up on stage and sing all his saliva runs out of his mouth followed by a bad breath. He also have an ulcer on his mouth and cheek because he is a heavy smoker.

3- ADRENOCEPTOR BLOCKING AGENTS (Beta blockers)

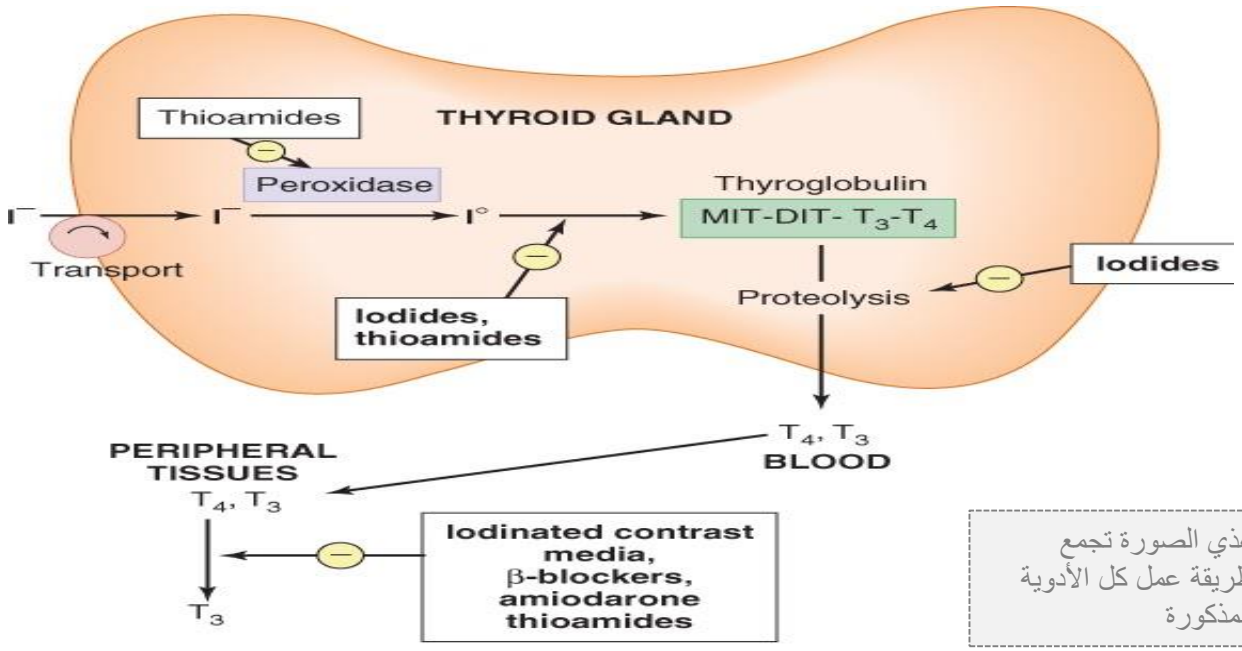
Propranolol, Atenolol , Metoprolol

M.O.A	Adjunctive therapy to relief the adrenergic symptoms of hyperthyroidism such as tremor, palpitation, heat intolerance and nervousness.
C.I	Propranolol is contraindicated in asthmatic patients (we have to ask the patient its very important)

4- RADIOACTIVE IODINE (RAI)

RadioActive Iodine (RAI)

M.O.A	• ^{131} I isotope (therapeutic effect due to emission of β rays) • Accumulates in the thyroid gland and destroys parenchymal cells, producing a long-term decrease in thyroid hormone levels.
Pharmacokinetics	• Clinical improvement may take 2-3 months • Half -life 5 days (it takes long time to give its effect) • Cross placenta & excreted in breast milk→ so it's not recommended in pregnancy • Easy to administer ,effective , painless and less expensive • Available as a solution or in capsules
indication	• Can be used As a diagnostic method • Hyperthyroidism mainly in old patients (above 40) less harmful effects • Graves, disease • Patients with toxic nodular goiter
Disadvantages	• High incidence of delayed hypothyroidism. most common • Large doses have cytotoxic actions (necrosis of the follicular cells followed by fibrosis) • May cause genetic damage • May cause leukemia & neoplasia



هذي الصورة تجمع طريقة عمل كل الأدوية المذكورة

Special conditions of hyperthyroidism

Thyrotoxicosis during pregnancy

- Better to start therapy **before** pregnancy with ^{131}I or subtotal thyroidectomy to avoid acute exacerbation during pregnancy
- During pregnancy :
  - Radioiodine is contraindicated.
  - **Propylthiouracil** is the drug of choice during pregnancy.

Thyroid Storm

- A sudden acute exacerbation of all of the symptoms of thyrotoxicosis, presenting as a life threatening syndrome.
- There is hyper metabolism, and excessive adrenergic activity, death may occur due to heart failure and shock.
- It is a medical emergency .

Management of Thyroid Storm

- should be treated in an ICU for close monitoring of vital signs and for access to invasive monitoring and inotropic support
- Correct electrolyte abnormalities, Treat cardiac arrhythmia (if present) & Aggressively control hyperthermia by applying ice packs
- Promptly administer antiadrenergic drugs (e.g. propranolol) to minimize sympathomimetic symptoms. (careful if he's asthmatic patient)
- High-dose Propylthiouracil (PTU) is preferred because of its early onset of action (risk of severe liver injury and acute liver failure)
- Administer iodine compounds (Lugol's iodine or potassium iodide) orally or via a nasogastric tube. due to its rapid effects
- Hydrocortisone 50 mg IV every 6 hours to prevent shock.
- Rarely, plasmapheresis has been used to treat thyroid storm يعني يشيلون البلازما ويصفونها ويشيلون الهرمونات اللي مو مرغوبة ويرجعون البلازما للجسم

Management of Graves' disease*

Severe Hyperthyroidism

1. [markedly elevated serum T_4 or T_3 very large goitre, > 4 times normal]
2. Definitive therapy with radioiodine preferred in adults
3. Normalization of thyroid function with anti-thyroid drugs before surgery in elderly patients and those with heart disease

Mild/moderate hyperthyroidism

1. [small or moderately enlarged thyroid; children or pregnant or lactating women]
2. Primary anti-thyroid drug therapy should be considered
3. Start methimazole, 5–30 mg/day, (PTU preferred in pregnant women)
4. Monitor thyroid function every 4–6 week until euthyroid state achieved
5. Discontinue drug therapy after 12–18
6. Monitor thyroid function every 2 months for 6 months, then less frequently

* If relapse: Definitive radioiodine therapy in adults (Second course of anti-thyroid drug therapy in children)

* If remission: Monitor thyroid function every 12 months indefinitely

Thyroidectomy

Sub-total thyroidectomy is the treatment of choice in very large gland or multinodular goiter

There is no particular sequence for managing hyperthyroidism , it depends on the manifestations and the doctors opinion.

* هذي السلايد تبين لكم متى استخدم كل دواء بس الشي اللي بيجي في الاختبار استخدام الأدوية اللي قلناها قبل (يعني ايش استخدم في الحمل وكذا)

summary

Thioamides

Propylthiouracil	Methimazole
Inhibit peroxidase enzyme →inhibiting the synthesis	
• In addition to inhibiting peroxidase, it blocks peripheral conversion of T4→T3 • Has a fast onset of action • Drug of choice in Pregnant + breastfeeding women • ADRs: Hepatitis , Vasculitis, Agranulocytosis	• More potent & longer effect • Crosses placenta& excreted in milk ↓ NOT recommended for pregnant & breastfeeding women • Drug of choice in adults and children • ARDs: Agranulocytosis , abnormal taste/smell

Iodine compounds

- Inhibit thyroid hormone synthesis & release
- Block peripheral conversion of T4→ T3

- Cause temporary remission of symptoms (No sustained effect)
- Used prior to thyroid surgery to ↓vascularity & size
- **NOT** used for pregnant women
- Long term use/toxic dose may produce Iodism symptoms

Radioactive iodine (RAI)

Accumulates in thyroid & destroys its parenchymal cells →thus it results in a long term decrease of thyroid hormones

- NOT used for pregnant + breastfeeding women
- Can be used a diagnostic method
- Used for: elder pt. >40 , graves disease , pt. with toxic nodular goiter
- Result in delayed HYPO-thyrodism & may cause cytotoxic actions if given in large doses " necrosis of follicular cells followed by fibrosis"

Beta blockers: Propranolol , Atenolol , Metoprolol

- Given alongside with hyperthyroidism treatments to manage the adrenergic symptoms (palpitations , tremor , heat intolerance , nervousness)
- propranolol is avoided in pt. with Asthma

MCQs

Q1: A 39 years old female who has heat intolerance, weight loss and excessive sweating. On examination her thyroid is enlarged and there is pretibial myxedema. She is diagnosed with graves disease, the doctors decide to give her propylthiouracil as anti-thyroid to control her case. What is the mechanism of action of this drug?

A- Decrease both vascularity & size of thyroid gland by inhibiting the mitosis.
B- Destroys the parenchymal cells of thyroid gland by beta rays.
C- Inhibit the peroxidase enzyme centrally in thyroid gland.

Q2: Patient with which one of the following drugs is need to be assessed with the thyroid function test frequently ?

A- Lithium. *B- Amiodarone.* *C- Both*

Q3:Which one of the following line of treatment of hyperthyroidism may safe the life of patient especially if he has tachycardia and sever palpitation a long with her hyperthyroidism ?

A- Thioamides. *B- Radioactive iodine.* *C- β-blockers*

Q4: Which one of the following describe the main mechanism of action of propylthiouracil ?
A- Block the Conversion T3 into T4 in the peripheral.
B- Destroys the parenchymal cells of thyroid gland by beta rays.
C- Inhibit the peroxidase enzyme centrally in thyroid gland.

Q5: What is the drug of choice in treatment of hyperthyroidism in pregnant women ?

A-Methimazole. *B- Propylthiouracil.* *C- Propranolol.*

Q6: Which drugs of Thioamides may affect and decrease the WBC and the patient prone to get infection easily ?

A-Methimazole. *B- Propylthiouracil.* *C- Both .*

Q7: Patient who had hyperthyroidism and used anti-thyroid drug, he developed inflammation of blood vessels and his laboratory finding shows positive for Anti-neutrophil cytoplasmic antibodies. After excluding the other causes the doctors suggest this is drug induced vasculitis. Which anti-thyroid drug is responsible for that ?

A-Methimazole. *B- Propylthiouracil.* *C- Both .*

Q8: : Which drugs of Thioamides may affect the taste sensation and the patient may complain abnormal sense of taste ?

A-Methimazole. *B- Propylthiouracil.* *C- Both .*

1. C
2. C
3. C
4. C
5. B
6. C
7. B
8. A

MCQs

Q9: Which one of the following is recommended to be used before thyroidectomy to decrease the possibility of bleeding from thyroid vessels ?

A- Thioamides. *B- Radioactive iodine.* *C*-Lugol's solution or (KI).

Q10: Which one of the following describe the mechanism of action of radioactive iodine ?

A- Decrease both vascularity & size of thyroid gland by inhibiting the mitosis.
B- Destroys the parenchymal cells of thyroid gland by beta rays.
C- Inhibit the peroxidase enzyme centrally in thyroid gland.

Q11:Which one of the following line of treatment of hyperthyroidism acting by destruction of thyroid's parenchyma due to emission of β rays ?

A- Thioamides. *B- Radioactive iodine.* *C-* Lugol's solution

Q12: Which one of the following can be used as diagnostic and therapeutic in case of hyperthyroidism ?

A- Thioamides. *B- Radioactive iodine.* *C-* Lugol's solution

Q13: 63 years old male who is diagnosed with hyperthyroidism which drug is the best and safest choice in his case?

A- Thioamides. *B- Radioactive iodine.* *C- Potassium iodide*

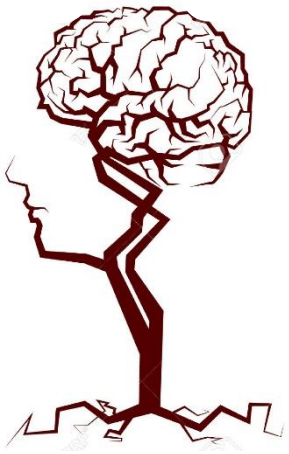
Q14: Why propylthiouracil is drug of choice in treatment of hyperthyroidism in pregnancy ?

A- It does Crosses placenta because it hydrophobic.
B- It is highly protein bound.
C-It has low incidence of delayed hypothyroidism.

Q15: Patient who had hyperthyroidism and used anti-thyroid drug, he suddenly developed thyroid storm which is emergency situation. He had sever palpitation and other excessive adrenergic activity. Which one of the following is considered as essential first step to be given in like this condition ?

A-Methimazole. *B- Radioactive iodine.* *C- propranolol.*

9. C
10. B
11. B
12. B
13. B
14. B
15. C



إِنَّ فِي ذَٰلِكَ لَآيَاتٍ لِّقَوْمٍ يَتَفَكَّرُونَ ﴿٣﴾

قادة فريق علم الأدوية :

- جومانا القحطاني - اللولو الصليهم

- فارس النفيسة

الشكر موصول لأعضاء الفريق المتميزين :

روان سعد القحطاني
شذا الغيهب
انوار العجمي
جواهر الخيال

عبدالرحمن الراشد

References :

1- 436 doctors slides