King Saud University

College of Medicine

2nd Year, Endocrine Block

PHARMACOLOGY 433

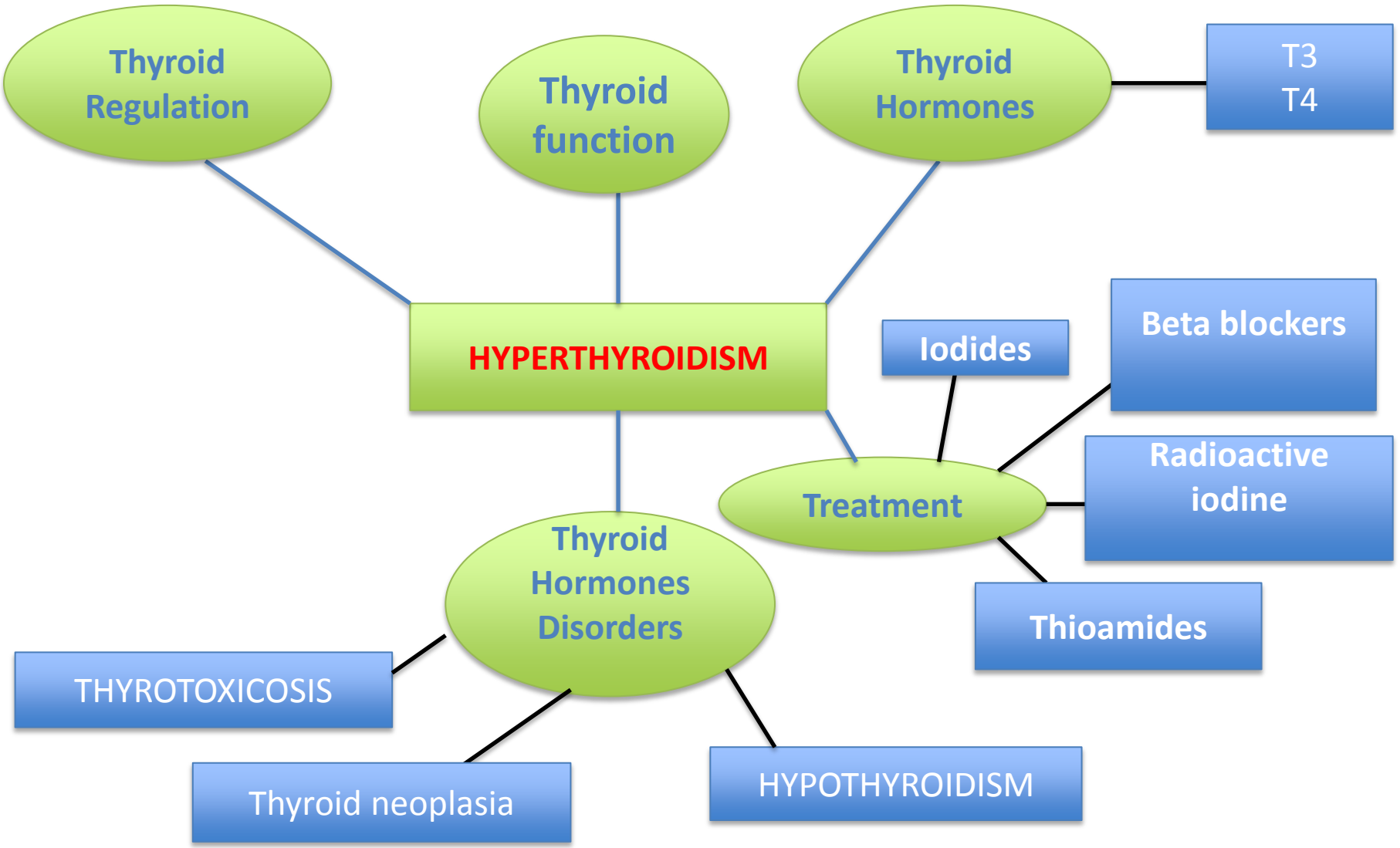
MED 433 Teams

LI-DRUGS USED IN HYPERTHYROIDISM

Objectives

- describe different classes of drugs used in hyperthyroidism and their mechanism of action
- understand their pharmacological effects, clinical uses and adverse effects.
- Recognize treatment of special cases such as hyperthyroidism during pregnancy, Graves' disease and thyroid storm

Mind map



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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 functions are :

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

Iodine Importantance :

- ✓ 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:
  - 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 peroxide

Thyroid Regulation

✓ TSH release is influenced by hypothalamic TRH, and by thyroid hormones themselves.

✓ Thyroid hormones exert negative feedback on TSH release at the level of the anterior pituitary.

- inhibition of TSH synthesis
- decrease in pituitary receptors for TRH

* TRH (thyrotropin releasing hormone)
* TSH (thyroid stimulating hormone or thyrotropin)

Thyroid Hormones Disorders

INTRODUCTION

THYROTOXICOSIS is Hypermetabolic state caused by thyroid hormone excess at the tissue level
While HYPERTHYROIDISM is Increased thyroid hormones synthesis and secretion

Causes of thyrotoxicosis

With high RAIU
- Graves diseases (60-80%)
- Multinodular goitre (14%)
- Adenomas / carcinomas

With low RAIU
- Thyroiditis
-Iodine-induced thyrotoxicosis drugs
(e.g. amiodarone) -radiografic contrast media

Features of Graves' Disease (Diffuse Toxic Goiter)

-Caused by thyroid stimulating immunoglobulins that stimulate TSH receptor , resulting in sustained thyroid over activity.
- Swelling and soft tissues of hands feet - Clubbing of fingers and toes
- Exophthalmos -5% have pretibial myxedema (thyroid dermopathy)

Features of Toxic Multi-nodular Goiter

- Second common cause of hyperthyroidism - have long standing goiter - Symptoms develop slowly

THYROTOXICOSIS

Symptoms:
- Irritability - Dysphoria
- sweating - Palpitations - Fatigue
- Weight loss & Diarrhea

Signs:
-Arrhythmias - Thyroid Enlargement
-Warm, moist skin - Exophtalmus - Pretibial myxedema

Treatment of Hyperthyroidism

- 1 Thioamides*
  - •Propylthiouracil (PTU)
  - •Methimazole
  - •Carbimazole*
- 2-Iodides
- 3-Radioactive iodine
- 4-Beta blockers
- 5-Surgery

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 T4 to T3 in peripheral tissues

*antithyroid drugs

* prodrug converted to the active metabolite methimazole

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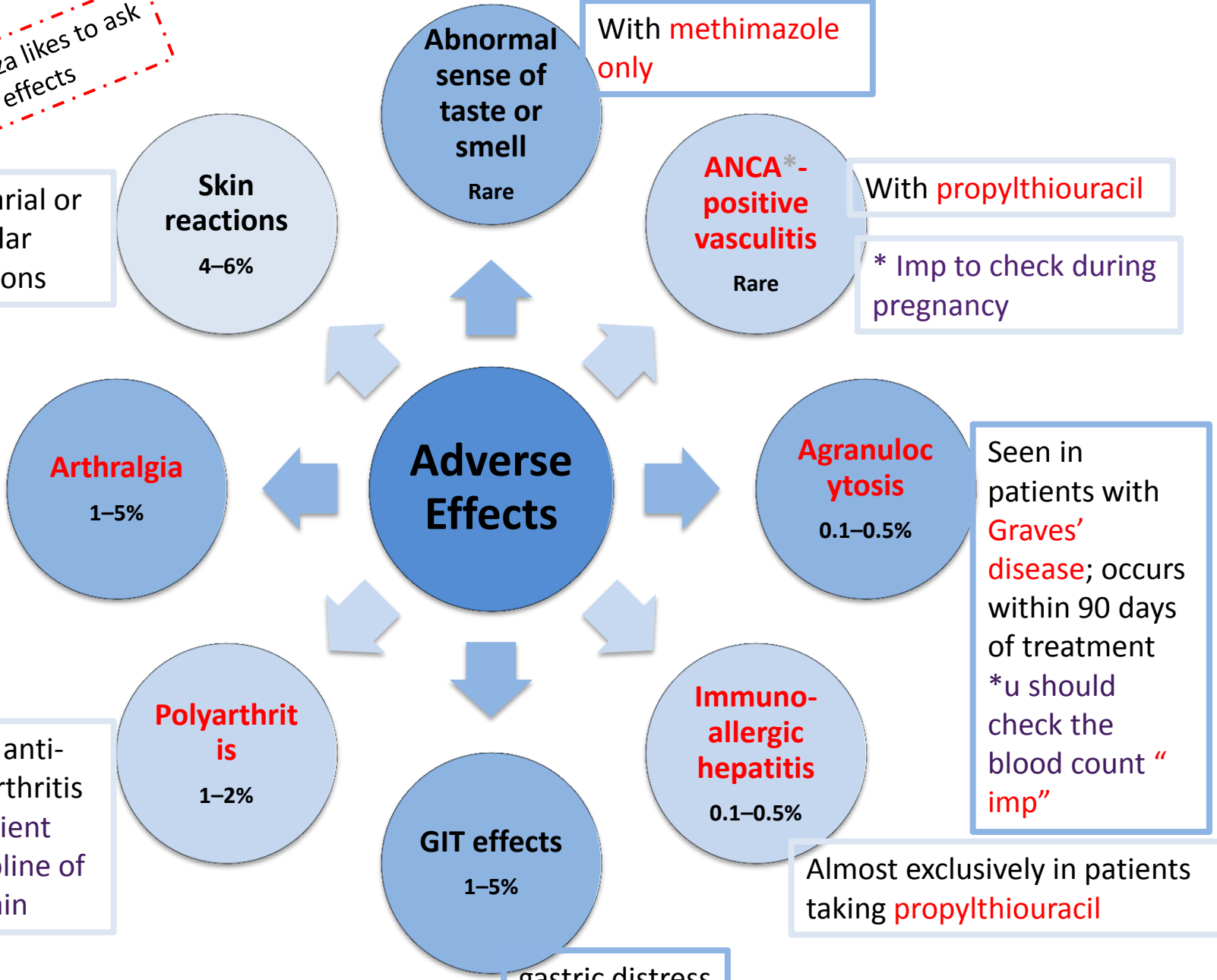
Pharmacokinetic comparison between Propylthiouracil and Methimazole

	Propylthiouracil	Methimazole
Absorption	Rapidly absorbed	Rapidly absorbed
Protein binding	80-90%	Most of the drug is free
accumulation	in thyroid	in thyroid
Excretion	Kidneys as inactive metabolite within 24 hrs	Excretion slow, 60-70% of drug is recovered in urine in 48 hrs
Half life	1.5 hrs (short)	6 hrs (long)
Administration	Every 6-8 hours	Every 8 hours
Pregnancy	crosses placenta "Recommended" in pregnancy (crossing placenta is less readily as it is highly protein bound)	Concentrated in Thyroid & crosses placenta "Not recommended" in pregnancy
Breast feeding	Less secreted in breast milk "Recommended"	secreted "Not recommended"

So important Dr.azza likes to ask about side effects



*anti neutrophil cytoplasmic antibodies

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2.IODINE

Iodine compounds	**Lugol's iodine, potassium iodid**
MOA	-Inhibit thyroid hormone synthesis and release " *it produces wolff chaikoff effect" - Block the peripheral conversion of T4 to T3 - The effect is not sustained (produce a temporary remission of symptoms)
Therapeutic uses	- Prior to thyroid surgery to decrease vascularity & size of the gland - Following radio active iodine therapy - Thyrotoxicosis " * to relief the symptoms rapidly "
Examples	Organic iodides as : **iopanoic acid or ipodate** *new in markets*
Precautions / toxicity	- Should not be used as a single therapy - Should not be used in pregnancy " * it has teratogenic effect " - May produce iodism * (Rare, as iodine is not much used now)

* Iodism Symptoms:

(skin rash , hypersalivation, oral ulcers, metallic taste, bad breath).

3. RADIOACTIVE IODINE (RAI)

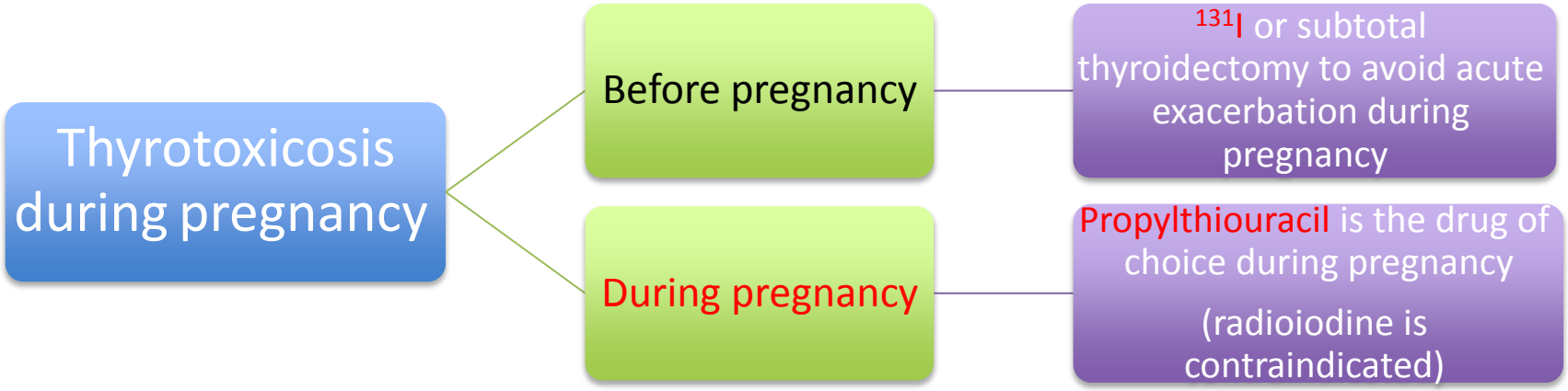
Drug	^{131}I isotope (therapeutic effect due to emission of β rays)
MOA	Accumulates in the thyroid gland and destroys parenchymal cells, producing a long-term decrease in thyroid hormone levels.
Pharmacokinetics	- Clinical improvement may take 2-3 months - Half -life 5 days - Cross placenta & excreted in breast milk - Easy to administer ,effective , painless and less expensive - Available as a solution or in capsules
Clinical uses	- Hyperthyroidism mainly in old patients (above 40) - Graves, disease - Patients with toxic nodular goiter - As a diagnostic
Disadvantages	- High incidence of delayed hypothyroidism - Large doses have cytotoxic actions (necrosis of the follicular cells followed by fibrosis) - May cause genetic damage " *it may cause infertility " - May cause leukemia & neoplasia

4. ADRENOCEPTOR BLOCKING AGENTS

Drug	Propranolol, Atenolol , Metoprolol
Use	**Adjunctive therapy** to relief the adrenergic symptoms of hyperthyroidism such as tremor, palpitation, heat intolerance and nervousness
Precautions	Propranolol is contraindicated in asthmatic patients

5. THYROIDECTOMY

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



(Better to start therapy before pregnancy)

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THYROID STORM (It is a medical emergency)

• 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.

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
- High-dose Propylthiouracil (PTU) is preferred because of its early onset of action (risk of severe liver injury and acute liver failure)" check liver function tests"
- Administer iodine compounds (Lugol's iodine or potassium iodide) orally or via a nasogastric tube
- Hydrocortisone 50 mg IV every 6 hours to prevent shock.
- Rarely, plasmapheresis* has been used to treat thyroid storm

*is the removal, treatment, and return of (components of) blood plasma from blood circulation

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Management of Hyperthyroidism due to Graves' disease

For Reading

Severe Hyperthyroidism

↓

[markedly elevated serum T4 or T3
very large goiter, >4 times normal]

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Definitive therapy with radioiodine preferred in adults

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Normalization of thyroid function with anti-thyroid drugs before surgery in elderly patients and those with heart disease

Mild/moderate hyperthyroidism

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[small or moderately enlarged thyroid; children or pregnant or lactating women]

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Primary anti-thyroid drug therapy should be considered

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Start methimazole, 5–30 mg/day,
(PTU preferred in pregnant women)

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Monitor thyroid function every 4–6 wk until euthyroid state achieved

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Discontinue drug therapy after 12–18 mo

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Monitor thyroid function every 2 mo for 6 mo, then less frequently

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Relapse

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Definitive radioiodine therapy in adults

(Second course of anti-thyroid drug therapy in children)

Remission

↓

Monitor thyroid function every 12 mo indefinitely

Summary

1-THIOAMIDES	Therapeutic uses	Adverse Effects
-Propylthiouracil (PTU)	1- anti-thyroid drug (drug of choice) 2- prefferd in pregnant women and breast feeding	-Skin reactions - Arthralgia - Polyarthritis - GIT effects Common Adverse Effects - ANCA-Positive-vasculitis And Immunoallergic hepatitis only in PTU Drug - Abnormal sense of taste and smell only in methimazole
- Methimazole - Carbimazole	1- anti-thyroid drug 2- Not recommended in pregnancy and Breast feeding.	

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

Therapeutic uses	Precautions / toxicity
1-Prior to thyroid surgery to decrease vascularity & size of the gland 2- Following radio active iodine therapy 3- Thyrotoxicosis	1-Should not be used as a single therapy. 2- Should not be used in pregnancy 3- May produce iodism (skin rash,hypersalivation, oral ulcers, metallic taste, bad breath).

3- RADIOACTIVE IODINE (RAI)

Therapeutic uses	Adverse Effects
1- Hyperthyroidism mainly in old patients (above 40) 2-Graves disease 3- Patients with toxic nodular goiter 4- As a diagnostic	1- delayed hypothyroidism 2- genetic damage 3-cytotoxic actions 4- leukemia & neoplasia

4- Beta Blocker (Propranolol ,Atnolol ,Metoprolol)	1-Use only relief the adrenergic symptoms . 2-Propranolol is contraindicated in asthmatic patients

Quiz yourself

1- which one of the following has high incidence of developing thyroid carcinoma :

a-Radioactive iodine
B-Anti-thyroid
C-Iodides

D-beta blockers

2- a pregnant women was diagnosed with thyrotoxicosis which one of the following is considered the drug of choice :
A-PTU
B-Mithemazol
C-Iodides
D-Propranolol

3- A patient has hyperthyroidism after treating him he developed vasculitis (ANCA+) which one of these drugs is most likely to have side affect :
A-PTU
B-Mithmazole
C-Liotrex
D-Levothyroxine

4- An asthmatic patient who was diagnosed with hyperthyroidism we prescribed him a drug to relief his adrenergic symptoms. What was that drug:
A-Propranolol
B-Metoprolol
C-iodide
D-methimazol

5-a 30-yaer old patient who has severe hyperthyroidism . to manage his case we should star treat him with :

A-mithemazol
B-Beta blockers
C-PTU
D-radioiodine

6- a 5-year old patient was diagnosed with mild hyperthyroidism which of the these drugs should we start with :
A-PTU
B-Mithemazole
C-Radioactive iodine
D-Propranolol

7- a patient have hyperthyroidism,he will undergo thyroidectomy. which one will help to decrease the size of his thyroid gland:

A-Ticlopidine

B-Potassium iodide
C-atenolo
D-Levothyroxine

8- a patient that was treated with hyperthyroidism then after few months he developed few side affect such as agranulocytosis and abnormal sense smell . which one of the following drugs can lead to such side affects :
A-Radioactive iodine
B-Anti-thyroid
C-Iodides
D-beta blockers

9-patient who developed thyrotoxicosis he was treated with drug that caused to him hypersalivation,oral ulceration and metallic taste which of these drugs can cause such side affect :
A-aspirin
B-potassium iodide
C-mithemazol
D-liotrex

Answers: 1-A 2-A 3-A 4-B 5-D 6-B 7-B 8-B 9-B

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We hope that we made this lecture easier for you
Good Luck !