

Treatment of hyperthyroidism

Drug	MOA & Pharmacokinetics	Indications	ADR& Contraindications, or precautions
<ul style="list-style-type: none"> ✓ Methimazole ✓ Propylthiouracil <p>Inhibit hormone synthesis onset of these agents are slow</p>	<ul style="list-style-type: none"> inhibiting thyroid peroxidase - mediated iodination of tyrosine residues in thyroglobulin They block coupling of iodotyrosine They block the conversion of T₄ to T₃ within the thyroid & in peripheral tissues 	<ul style="list-style-type: none"> Cutaneous reactions (urticaria , maculopapular rash pruritic very common) Arthralgia (antithyroid arthritis syndrome) GI upset , Hepatotoxicity (cholestatic jaundice mainly with methimazole), lymphadenopathy agranulocytosis which very rare and most dangerous There is cross sensitivity between propylthiouracil and methimazole. 	
<p>2-Iodides</p> <ul style="list-style-type: none"> Are not used in the routine treatment of hyperthyroidism because of paradoxical(contradictory) increase in hormone release with prolonged use. Organic iodides as iopanoic acid or ipodate are used commonly 	<ul style="list-style-type: none"> Possess multiple effects on thyroid gland Block the peripheral conversion of T₄ to T₃ & inhibit hormone release. Produces rapid improvement in thyrotoxic symptoms within 2-7 days 	<ul style="list-style-type: none"> Thyroid storm. Adjunctive therapy before surgery for Graves' disease to reduce gland size and vascularity. 	<ul style="list-style-type: none"> Increases the intraglandular stores of iodine which delays the effect of thioamides and prevents use of radioactive iodine. Should not be used as a single therapy Should not be used in pregnancy May produce iodism (aciform rash, swelling of salivary glands, mucous membrane ulceration, metallic taste bleeding disorders and rarely anaphylaxis).
<p>3-RADIOACTIVE IODINE ¹³¹I isotope</p> <ul style="list-style-type: none"> Rapidly absorbed, concentrated in thyroid gland and stored in follicles. Easy to administer ,effective , painless and less expensive 	<ul style="list-style-type: none"> emission of β rays that damage the thyroid Rapidly absorbed, concentrated in thyroid gland and stored in follicles. Half -life 5 days Cross placenta & excreted in breast milk Available as a solution or in capsules 	<ul style="list-style-type: none"> ❖ Hyperthyroidism mainly in old patients (above 40) ❖ Graves' disease ❖ Patients with toxic nodular goiter ❖ Diagnostic uses 	<ul style="list-style-type: none"> High incidence of delayed hypothyroidism Large doses have cytotoxic actions (necrosis of the follicular cells followed by fibrosis) May cause genetic damage May cause leukemia & neoplasia (carcinogenic) -Should not be given to pregnant or nursing mothers
4-ADRENOCEPTOR BLOCKING AGENTS: Propranolol			Contraindicated in asthmatic patients

Drugs used in Hypothyroidism

-Daily dose of a synthetic thyroid hormone preparations

-Serum TSH is the reliable guide to adjust thyroxine (thyroid hormone) dose

<p>L-LEVOTHYROXINE:(T₄)</p> <p>This is the preparation of choice for thyroid replacement and suppression therapy, because it is stable and has a long (7 days) half life, to be administered once daily.</p>	<ul style="list-style-type: none"> Oral preparations available are from 0.025 to 0.3 mg tablets Absorption is increased when hormone is given on empty stomach For parental use 200-500µg (100µg/ml when reconstituted) for injection. <p>In long standing condition, in old patients and in patients with cardiac disease, treatment is started with reduced dosage. Can restore normal thyroid levels within 2-3 weeks. levothyroxine is given in a dose of 12.5 – 25 µg/day for two weeks and then increasing it after every two weeks.</p>	<p>ADVERSE EFFECTS OF OVER DOSE CHILDREN :</p> <ul style="list-style-type: none"> Restlessness, insomnia, accelerated bone maturation. <p>ADULTS :</p> <ul style="list-style-type: none"> Agitation , heat intolerance , pain (headache, muscle pain) Intestinal & metabolic symptoms (change in appetite, diarrhea, weight loss) <p>Adverse effects of under-dosing</p> <ul style="list-style-type: none"> Sluggishness Mental dullness Feeling cold Muscle cramps
<p>2-Liothyronine(T₃)</p> <ul style="list-style-type: none"> More potent (3-4 times) and rapid than levothyroxine but has a short half life is not recommended for routine replacement therapy, it requires multiple daily doses. It should be avoided in cardiac patients. It is best used for short -term suppression of TSH. Oral preparation available are 5-50µg tablets For parental use 10µg/ml 		

Pharmacokinetic comparison between Propylthiouracil and Methimazole		
Absorption accumulation Excretion	Rapidly absorbed from GIT	Same
	In thyroid	Similar
	Kidneys as inactive metabolite within 24 hrs	Excretion slow, 60-70% of drug is recovered in urine in 48 hrs
Absorption Protein binding Half life	Rapidly absorbed from GIT	Same
	80-90% is bound	Most of drug is free
	1.5-2hrs (short half-life)	6 hrs (long half-life)
Administration	Every 6-8 hrs	As a single dose
Pregnancy	Preferred, though cross placenta and is conc. in fetal thyroid but is highly protein bound, crossing placenta is less readily	Cross placenta and concentrated by fetal thyroid Not recommended
Breastfeeding	Less secreted in breast milk	secreted
	Recommended	Not recommended

Management of Grave's disease

- Drug therapy such as **methimazole** and **propylthiouracil**
- Surgical thyroidectomy
- Destruction of the gland with **radioactive iodine**

In young patient with small gland and mild disease

- Methimazole / propylthiouracil until disease undergoes spontaneous remission.
- this may take 1-2 years with 60-70 % relapse.
- therapy is started with large divided doses, then shifted to maintenance therapy with single daily dose.
- **Propylthiouracil** is better than **methimazole**.
- Reactivation of the autoimmune process may occur lead to **increase in TSH** and stimulation of thyroid, this can be prevented by addition of **levothyroxine (T4)**.

Special cases of Hyperthyroidism

THYROID STORM:

- It is 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**.
- Vigorous management is mandatory. **Propranolol** 1-2mg slow I/V or 40-80 mg orally every 6 hours
- **Potassium iodide** 10 drops orally daily or
- **Propylthiouracil** 250 mg orally every six hours or 400 mg every six hours rectally.
- **Hydrocortisone** 50 mg I/V every 6 hours to prevent shock.

Thyrotoxicosis during pregnancy

- Definitive therapy with ¹³¹I or subtotal thyroidectomy prior to pregnancy to avoid acute exacerbation during pregnancy or after delivery
- During pregnancy radioiodine is contraindicated.
- Propylthiouracil is better choice during pregnancy. Dose must be kept minimum i.e., <300 mg daily.

Conditions that cause a decrease in serum binding proteins

Androgens, Old patients, Nephrosis, Cirrhosis

Medications that reduce the absorption of thyroid hormone from intestine

- ✓ Cholestyramine
- ✓ Aluminum containing antacids
- ✓ Calcium preparations
- ✓ Ferrous preparations

Medications that accelerate metabolism of thyroid hormones

- ✓ Rifampin
- ✓ Phenytoin
- ✓ Phenobarbital
- ✓ Oral hypoglycemic drugs

Conditions that cause an increase in serum binding proteins

High estrogen states (pregnancy, oral contraceptive use, postmenopausal estrogen replacement)
The dosage of levothyroxin must be increased

Summary:

- ✓ **Thioamides** (e.g **Methimazole** or **Propylthiouracil**) inhibit thyroid **peroxidase**- mediated iodination. (They block the synthesis of new thyroid hormones)
- ✓ **Propylthiouracil** and (to a much lesser extent) **methimazole** inhibit the peripheral & **thyroid deiodination of T₄ and T₃** (weak effect)
- ✓ Since the **synthesis** rather than the **release** of hormones is affected, the onset of these **agents are slow**
- ✓ **Propylthiouracil** is highly protein bound, has a short half-life, and is preferred in pregnancy and lactation; however, **Methimazole** is mostly free in the circulation, and has a long half-life.
- ✓ ADRs includes **maculopapular rash**, **Arthralgia**, **cholestatic jaundice (mainly with methimazole)**, and **Agranulocytosis** (rare but dangerous)
- ✓ **This reaction** is usually **reversible** when the drug is immediately discontinued.
- ✓ **Colony stimulating factor** is administered to hasten the recovery of the **granulocytes**
- ✓ There is **cross sensitivity** between **propylthiouracil** and **methimazole**.
- ✓ **Iodides** Inhibit hormone release by probably **inhibiting both iodination and proteolysis of thyroglobulin**
- ✓ Since they inhibit the release rather than synthesis of T₃ & T₄ they **are rapidly acting**
- ✓ They also Block the peripheral conversion of **T₄ to T₃**
- ✓ **Clinical uses:** as adjunctive therapy, before **surgery** to reduce size & vascularity of hyperplastic gland.
- ✓ the gland **will escape** from **iodide block in 2-8 weeks**, this may produce severe exacerbation of thyrotoxicosis in an iodinated – enriched gland
- ✓ Produces increase in the **intraglandular stores of iodine** which **delays the effect of thioamides** and **prevents use of radioactive iodine**; therefore, iodides should be initiated after thioamides, and should not be used with radioactive iodine.
- ✓ **They may produce Iodism** (acneiform rash, swelling of salivary glands, mucous membrane ulcerations, metallic taste ,bleeding disorders and rarely anaphylaxis).
- ✓ They Should be **avoided in pregnancy**
- ✓ **Radioactive Iodine** therapeutic effect depends on emission **of β rays that specifically damage the thyroid.**
- ✓ They have **High incidence** of delayed **hypothyroidism**
- ✓ Large doses have cytotoxic actions (necrosis of the follicular cells followed by fibrosis)
- ✓ **Adrenoceptor Blocking Agents:** E.g. **Propranolol**, **Atenolol** are used to Relief the adrenergic symptoms of hyperthyroidism
- ✓ Contraindicated in **asthmatic patients**, **Diltiazem A Ca channel blocker is used instead.**
- ✓ A near-total thyroidectomy is the treatment of choice in **very large gland or multinodular goiter**
 - ✓ To treat the hypothyroidism the replacement therapy is appropriate **And LEVOTHYROXINE(T₄) is the preparation of choice** , also we can use Serum TSH as the reliable guide to adjust thyroxin dose.
- ✓ **LEVOTHYROXINE(T₄)** has long half-life so we use it as routine replacement therapy however Liothyronine(T₃) has short half-life and not recommended as a routine therapy. For the pregnant women we use **LEVOTHYROXINE(T₄)** .
 - ✓ **LEVOTHYROXINE(T₄)** has Oral preparations used as routine therapy which has best if it was given on empty stomach also it has parenteral preparation for emergency situations , however **Liothyronine(T₃)** is just used for short –term suppression of TSH (acute emergency) but be aware it should be avoided with cardiac patient, since it has a more potent effect
 - ✓ The adverse effect of using **LEVOTHYROXINE(T₄)** differs according to the dosing (over –below the therapeutic dose)
 - ❖ over dosing in adult same like any toxicities of other drugs but **in children (CNS disorders mainly like : Restlessness, insomnia) and accelerated bone maturation.**
 - ❖ under-dosing **it's more dangerous including** :Sluggishness ,Mental dullness, Feeling cold and Muscle cramps (**pain**)