Endocrin E system

Pharmacology

Sheet | Slide | Past Papers | Summary

Number: 3

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• I'll include the slides that the doctor read them (They are highlighted). Other slides will not be included.

• The doctor may repeat some information mentioned in the previous lectures. Don't worry it will help you.

So, let's get started!!

Some notes from the last lecture:

- We know that thyroid gland is very important, and it produces T_3,T_4 hormones.
- The more iodine you have the more T_3,T_4 you are going to produce.
- Iodine is converted to organic iodine by peroxidase enzyme then it gets incorporated by tyrosine and become iodothyronine to end up by T_3 or T_4 which they are at the end stored in the thyroid gland.
- Remember that T_4 is secreted then it is converted to T_3 in small amounts (that doesn't mean that T_4 don't have a function, it has some activity).
- The Half-life for T_4 is (7 days) while it is (1 day) for T_3.
- In case of hypothyroidism we resort to replacement especially T_4.
- We give thyroxin as a treatment for hypothyroidism.

T_3 replacement is used in rare cases like if there is a real hypothyroidism (deterioration in the patient status or he/she enters a coma), so T_3 is recommended in emergencies as it acts fast, however T_4 takes long time.

- Why don't we use T_3 in all cases?

Because of the high potency of T_3 we are afraid of heart complications but how?

We know that thyroid hormones sensitize β-receptors towards adrenalin and noradrenalin and as a result many things gonna be affected by that. for example, we see that the patients with hyperthyroidism usually suffer from sympathetic activation.

- T_4 is preferable and much more common than T_3 because it gets converted to T_3 slowly, so the chance of sensitization is less.

What happens if sensitization of β-receptors occurs ?

That may develop a real tachycardia or arrhythmia.

To conclude: T_4 is used as a replacement thereby of hypothyroidism and sometimes we use T_3 in some emergencies.

Hyperthyroidism

The more common disease especially in ladies (4:1 female:

male). How can we deal with hyperthyroidism?

By two ways:

1- Drugs (anti-thyroid drugs).

OR

2- Thyroidectomy either by surgery or by radiation.

• Surgery is used if there is no effective drug could be used.

NOTE from the Dr: there would be some harm when we go for Thyroidectomy, one of them is your patient would need a replacement all of his life due to losing his gland so that surgery would the last choice.

• Theoretically there is 50% chances to be cured from hyperthyroidism from using drugs only. The drugs usually used for two years then we stop it gradually.

- The drugs we can use as mentioned in the last lecture are: **Thionamides**, **radioactive iodine**, **iodide (we use it surgery)**, **iodinated contrast media** (we will not explain them even they are present in the slides) and **β-blockers** for alleviation of the symptoms caused by sensitization of **β**-receptors in sympathetic system.

Let's go deeper…

Major anti-thyroid drugs:

Thionamides:

- Methimazole
- Propylthiouracil (PTU)
- Carbimazole (prodrug of methimazole)

Methimazole is prescribed for 99% of the cases of hyperthyroidism in children and adults. It is 10 times more potent than PTU.

PTU is used mainly in three cases:

1 – in pregnancy especially first trimester.

2 – thyroid storm (thyrotoxication- means that T_3 & T_4 in all over the body).

3 – Patients who experience adverse reactions to methimazole.

Pharmacodynamics

1. Prevention of thyroid hormone synthesis by inhibiting thyroid peroxidase and blockade of iodine organification.

2. Block coupling of iodotyrosines.

3. PTU also blocks the peripheral conversion of T4 into T3 by 5'-deiodinase.

• **The effect is slow requiring 3-4 weeks before stores of T4 are depleted.** (read the last paragraph in sheet 2 to understand this point)

We give methimazole at different doses for example, the first 4-6 weeks we give the patients up to 40 mg/day. After improvement in the situation we reduce the dose to 20/25/30… according to variables and the treatment continues up to two years, then we decrease it gradually.

t½:

PTU : 1.5 hours ⟹ given every 6-8 hours

Methimazole : 6 hours ⟹ given once daily

Both (methimazole and PTU) can cross placenta and accumulate in fetal thyroid and cause hypothyroidism, but PTU less readily so because of high protein binding that's why PTU is the drug of choice in pregnancy. Also, it is not secreted in sufficient quantity in breast milk to preclude breast feeding.

** The calculated half-life for PTU and Methimazole is not real **t½** they aren't excreted out of the body rather they are trapped in the thyroid gland, so the real half-life and the one relative to your administration is

present in the thyroid gland and concentrated there. The real half-life could reach 4 times the plasma half-life.

Note from Dr: in the emergency situation (in Thyroid storm cases) the drug of choice is PTU because it reaches our target very quickly and has quick response (1.5h). Also, it inhibits the synthesis of thyroid glands.

Why the patients don't use anti-thyroid drugs for all life?

Because of the side effects. What are they?

Adverse effects:

Occur in 3-12% of patients (they are rare but fatal).

1- Most reactions occur early, especially **nausea** and **gastrointestinal distress.**

2- **Altered sense of taste** or smell may occur with methimazole.

3- **Maculopapular pruritic** rash with or without fever – most common (4-6%).

4- Rare adverse effects (not for memorizing) include an urticarial rash, vasculitis and lupus-like reaction.

5- Severe may be **fatal hepatitis** reported with propylthiouracil, so it should be avoided in children and adults.

6- **Cholestatic jaundice** is more common with methimazole than propylthiouracil.

7- **Agranulocytosis** (low WBC in the blood (< 500 cells/mm3) and this is a very dangerous condition (the patients have 50% chance of dying).

- Infrequent (0.1 – 0.5 % of patients) but potentially fatal, and rapidly reversible.
- More frequent in the elderly and at doses more than 40 mg. (dose dependant).
- G-CSF may speed recovery of granulocytes.
- Cross-sensitivity between PTU and methimazole is ~ 50%. What does that mean?

** If a patient has agranulocytosis (it is real threaten side effect) from PTU he/she has 50% to have agranulocytosis from methimazole and vice versa.

According to what was mentioned we have to do WBC count in those patients every 6 months and in ladies we do it every 3 months.

We said that we give the patients the drug for two years now suppose that you have two groups the first one cure from the disease and the second one does not.

Then what to do?

The first group you must give them beta blockers to avoid of happening arrhythmia or the recurrence of the disease.

For the second group we have two options:

1- Iodine radiation: I^{131} instead of I^{128} which makes emission of radiation in the thyroid gland.
2- Surgery: we call it Subtotal thyroidectomy.

Radioactive iodine

Administered orally as NaI^{131} solution as one shot.

Rapidly absorbed (100% absorbed) concentrated by the thyroid gland and incorporated into storage follicles.

Its effect is due to emission of β-rays to the thyroid cells and the nearby cells which are parathyroid cells (t½ ~ 5 days, penetration 400-2000 μm).

does this emission affect other part of our body? And why?

No, because the penetration is weak, so its effect is exclusive for thyroid gland (it could affect parathyroid glands, but it is very rare to happen).

The result ⟹ the thyroid parenchyma is destroyed within 6-12 weeks.

Advantages:

1. Easy administration
2. Effectiveness
3. Low expense
4. Painless

5. All risks of surgery are avoided

Disadvantages:

**Major complication is hypothyroidism (80% of patients) which requires T4 replacement for all his life.

**Fears of radiation-induced genetic damage, leukaemia and neoplasia which made some clinics to restrict its use for patients < 40 years of age. (No evidence over 50 years of use).

** Should not be administered to pregnant women or nursing mothers because they emit radiation.

The patients advised to stay away from people approximately 3 meters for 5 days (which is the half-life of I^{131} and then all iodine is present in the thyroid gland).

Let's go back to the second choice which is **surgery**.

Because thyroidectomy is a hard operation we need something to help the surgent. That thing is iodide?? But how? Iodide itself makes hyperthyroidism. When you give patients iodide you activate making more T3 and T4 but what's happening here is that we give them a high dose which blocks making thyroid hormones.

(Low dose activates thyroid gland, but high dose blocks it).

• At pharmacological doses (> 6 mg/day), the major action is inhibition of organification (of iodine) and thyroid hormone release, possibly by inhibition of thyroglobulin proteolysis. rapid improvement in 2-7 days.

• Reduces vascularity, size, fragility of the hyperplastic thyroid glands

◊ useful for preoperative preparation for surgery (we give it two weeks before the operation [thyroidectomy])

Disadvantages:

1. Increased intraglandular stores of iodine:

A. Delay the onset of thionamide therapy.

Should be initiated after onset of thionamide therapy.

B. Prevent use of radioactive iodine therapy for several weeks.

Should be avoided if treatment with I^{131} is planned.

2. Should not be used alone for treatment of hyperthyroidism, because the gland will escape from iodine block in 2-8 weeks.

What to do exactly:

If we decide to do thyroidectomy (8 weeks before operation) we give the patient six weeks of methimazole (with beta blockers) after the six weeks we stop methimazole (continue using beta blocker) then we give iodides for two weeks, then you do the surgery. Note that after giving iodide you must do the surgery you can't ignore it for any reason because if you don't do the surgery there will be thyrotoxication (usually the patient Sign an agreement to do the surgery after the doctor decide to do it)

3. Its withdrawal may precipitate thyrotoxicosis because the gland is iodine- enriched.

4. Should be avoided during pregnancy, because it may produce fetal goiter and hypo- or hyperthyroidism.

Toxicity:

• Iodism: uncommon, reversible: Acneiform rash, swollen salivary glands, mucus membrane ulceration, conjunctivitis, rhinorrhea, drug fever, metallic taste, bleeding, anaphylactoid reactions.

Beta adrenergic blockers:

Remember that β-1 and β-2 gonna be sensitized so we chose non-selective type of adrenergic receptors like propranolol to block all receptors.

We chose propranolol also because it prevents the conversion of T4 to T3. This action also done by other drugs like glucocorticoids.

After surgery we can use beta blocker. Remember that we call it subtotal thyroidectomy, so the sensitization of beta receptors may continue after surgery for years. So, β-blocker is important in our disease.

Propranolol is a drug without intrinsic sympathomimetic activity.

Sympathomimetic means its action is similar to sympathetic

Note from the Dr:

(Those are partial agonists they bind to the receptors and activate them. However this activation won't be as strong as noradrenalin "endogenous activator" or potent activating. So by this it will prevent the strong activator to bind to the receptors to produce full activity- we will get more information about it next year as the Dr. said).

Many manifestations of thyrotoxicosis are due to hyperactivity of the sympathetic nervous system, which may be due to increased number of β-adrenergic receptors or amplification of β-adrenergic receptor signal (cAMP).

- Do not typically alter thyroid hormone levels.
- They also inhibit 5'-deiodinase which converts T4 into T3.
- Control tachycardia, hypertension and atrial fibrillation associated with hyperthyroidism.
- In patients with bronchial asthma or when β-adrenergic blockers are contraindicated, diltiazem is an alternative.