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Clinical pharmacology of thyroid and antithyroid drugs

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Abstract

Autoimmune diseases accompanied by the development of hypothyroidism (Hashimoto's thyroiditis) and hyperthyroidism (Graves' disease) are one of the most common disorders of the thyroid gland. Hypothyroidism is a clinical syndrome that occurs as a result of thyroid hormone deficiency. Hyperthyroidism is excessive activity of the thyroid gland accompanied by hypersecretion of thyroid hormones. In simple terms, to achieve a euthyroid state in both clinical syndromes, two drugs are (most commonly) used - levothyroxine (hypothyroidism) and thioamide (hyperthyroidism). While it may seem simple, during the treatment, which is life-long in the case of hypothyroidism, patients should actually be carefully monitored, with the adjustment of the drug dose and the inclusion of other drugs for the treatment of comorbidities.

Key words: Hashimoto's thyroiditis, Graves' disease, levothyroxine, thiamazole, propylthiouracil

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Synthesis, mechanism of action, and effects of thyroid hormones

Diseases of the thyroid gland are among the most common diseases today, and among them the two most frequent ones are autoimmune diseases accompanied by the development of hypothyroidism (Hashimoto's thyroiditis) and hyperthyroidism (Graves' disease). The thyroid gland produces two thyroid hormones: thyroxine, T4, and to a lesser extent triiodothyronine, T3.

The functional unit of the thyroid gland is the follicle or acinus. The steps in the synthesis, storage and secretion of thyroid hormones are shown in Figure 1. Listed in detail, they involve:

- uptake of iodide by follicle cells
- oxidation of iodide and iodination of tyrosine residues in thyroglobulin (Tg) colloid in the presence of thyroid peroxidase (TPO)
- coupling of L-mono-iodotyrosine and L-di-iodotyrosine in the presence of TPO
- uptake of T_3 and T_4 (with Tg) into follicle epithelial cells, where T_3 and T_4 are released from Tg under lysosomal proteolytic enzymes and secreted into the circulation (1).

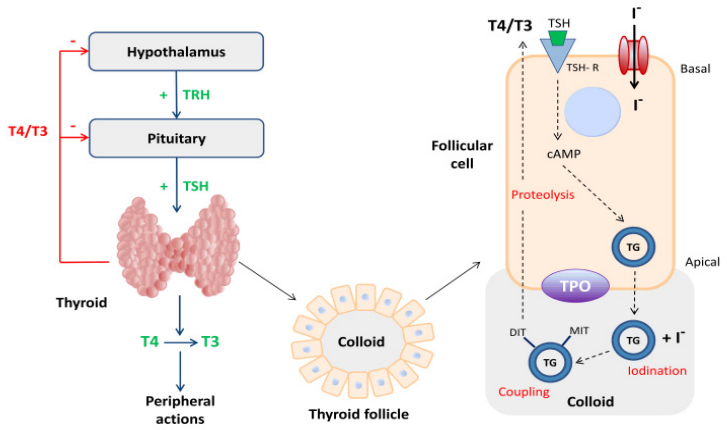

Figure 1. **Regulation of thyroid hormone synthesis. TG – thyroglobulin; TSH-R – thyroid-stimulating hormone receptor; TPO – thyroid peroxidase; MIT – monoiodotyrosine; DIT – diiodotyrosine; I – iodide; TRH – thyrotropin-releasing hormone; TSH – thyroid-stimulating hormone**

Slika 1. **Regulacija sinteze tiroidnih hormona. TG – tireoglobulin; TSH-R – receptor za tireostimulirajući hormon; TPO – tiroidna peroksidaza; MIT – monojodotirozin; DIT – dijodotirozin; I – jodid; TRH – tireotropin oslobađajući hormon; TSH – tireostimulirajući hormon**

The thyroid gland secretes almost 20 times more T_4 than T_3. T_4 and T_3 are mostly bound to thyroxine-binding globulin in plasma. Only the free fractions (FT_4 and FT_3) of hormones are available for action in tissues.

The secretion of thyroid hormones is under the control of the hypothalamic-pituitary axis. Thyrotropin-releasing hormone (TRH) from the hypothalamus stimulates the secretion of thyroid-stimulating hormone (TSH) from the adenohypophysis, while thyroid hormones act on the hypothalamus/pituitary to reduce TRH/TSH secretion (by a negative feedback mechanism) (Fig. 1).

Mechanism of action and effects of thyroid hormones

Most of the effects of thyroid hormones are the consequence of the activation of specific nuclear receptors of the target cells. Receptors for thyroid hormones (TRs) are present in almost all tissues, and are especially numerous in the brain, kidneys, gonads, liver, gastrointestinal tract, heart, skeletal muscles and pituitary gland. Upon entering the cells, T_4 is deiodinated by the deiodinase enzyme and T_3, which has a higher affinity for receptors, is formed. The TRs contain a central DNA-binding domain and a C-terminal ligand-binding domain. They bind to specific DNA sequences, termed *thyroid response elements*, in the promoter regions of target genes. The receptors bind as homodimers or, more commonly, as heterodimers with retinoic acid X receptors. The activated receptor can either stimulate or inhibit gene transcription, depending on the nature of the regulatory elements in the target gene (1).

Thyroid hormones affect metabolism and growth and development. The main role of thyroid hormones in adults is to regulate the metabolism of carbohydrates, fats and proteins with an increase in consumption of O_2 and heat production. The use of thyroid hormones results in an increase in the heart rate, with a tendency towards arrhythmias, especially atrial fibrillation, as well as a positive inotropic effect. In infants and children, thyroid hormones are necessary for the development of central nervous and reproductive systems, as well as for normal growth (directly and indirectly through effects on growth hormone) (1, 2).

Hypothyroidism

Pathogenesis

Iodine deficiency is the most common cause of hypothyroidism in the world. In areas where the supply of iodine is sufficient, the most common cause of hypothyroidism is an autoimmune disease, Hashimoto's thyroiditis. The thyroid lymphocytic infiltrate in Hashimoto's thyroiditis is composed of activated T cells, as well as B cells. Thyroid cell destruction is primarily mediated by the CD8+ cytotoxic T cells, but local production of cytokines, such as tumor necrosis factor, interleukin-1, and interferon γ derived from inflammatory infiltrate, may make thyroid cells more susceptible to apoptosis. Activated B lymphocytes produce antithyroid antibodies directed against TPO and Tg. These antibodies are less important for the pathogenesis of the disease, but they are useful

clinical markers of autoimmune thyroid diseases. Certain patients with Hashimoto's thyroiditis are also positive for antibodies against the TSH receptor which, unlike the antibodies seen in Graves' disease, block the effects of TSH. As Hashimoto's thyroiditis gradually progresses, fibrosis becomes more pronounced, thyroid follicles disappear, and *atrophic thyroiditis* develops, which represents the final stage of Hashimoto's thyroiditis, rather than a separate clinical entity (3-6).

Hypothyroidism can be with or without goiter. Fertility in hypothyroidism is reduced and the frequency of miscarriage is increased (6).

Diagnosis of hypothyroidism

The diagnosis of hypothyroidism is made based on the determination of the concentration of TSH and unbound T_4 (FT_4) in serum. In *primary hypothyroidism*, the TSH level is elevated, and FT_4 level can be reduced (*clinical hypothyroidism*) or normal (*subclinical hypothyroidism*). The importance of determining the TSH level is much greater than determining unbound T_4, because subclinical hypothyroidism cannot be detected on the basis of unbound T_4 level. Circulating FT_3 is normal in about 25% of patients, due to the adaptive deiodinase response to hypothyroidism. T_3 measurement is not indicated. For a differential diagnosis of Hashimoto's thyroiditis, an ultrasound examination is performed, which shows a heterogeneous enlargement of the thyroid gland, in contrast to multinodular goiter and thyroid cancer. AntiTPO and antiTg antibodies are also used in diagnosis (4-7).

In *secondary hypothyroidism*, the TSH level may be low, normal, or slightly elevated, while FT_4 level is decreased. People with secondary hypothyroidism usually also have a deficit of other pituitary hormones, so it is important to determine the severity of hypopituitarism before starting thyroid hormone therapy. It is especially important to determine whether there is a need for replacement therapy with glucocorticoids and to correct it (6).

Treatment of hypothyroidism

Clinical hypothyroidism

Levothyroxine is the drug of choice for lifelong treatment of primary (clinical) hypothyroidism. Although T_3 has greater biological activity than T_4, levothyroxine replacement therapy provides a stable reservoir of T_4 that is readily converted to T_3. Levothyroxine has a long plasma half-life (7 days), and is given as a sodium salt in a single daily oral dose. Liothyronine has a much faster and shorter action compared to levothyroxine and is used intravenously in life-threatening hypothyroidism (*myxedema coma - a rare form of decompensated hypothyroidism)*, when rapid intervention is needed (2-7).

Many factors can influence the dose of levothyroxine, such as: *body weight*, *etiology of hypothyroidism*, *age*, *comorbidities, and interaction with other drugs*. Patients who developed hypothyroidism as a result of thyroidectomy require higher doses than

those with Hashimoto's thyroiditis (in whom the thyroid gland retains some activity). The required dose of levothyroxine may change over time, since the need for levothyroxine increases as the destruction of the thyroid gland gradually progresses. With age, the required dose of levothyroxine decreases (1-7).

If there is residual thyroid function and the patient is elderly or has an ischemic heart disease, it is recommended to start with 25 μg of levothyroxine, which can be gradually increased. If there is no residual thyroid function and the patient is younger and without ischemic heart disease, therapy can be started with a full replacement daily dose of 1.6 μg/kg/day, which is typically 100-150 μg. The success of substitution therapy is monitored by measuring TSH every 6-8 weeks at the beginning of therapy. When a stable euthyroid state is achieved, it is sufficient to monitor TSH each 6-12 months. Therefore, the dose of levothyroxine is adjusted based on TSH levels, with the goal of treatment being between 0.2-4.2 mIU/L. In elderly patients, it is acceptable for the TSH level to be slightly higher (4-6 mIU/L). The dose of levothyroxine should be increased in the case of malabsorption (celiac disease, small bowel surgery), use of estrogen hormones that increase thyroxine binding-globulin, the main transport protein for thyroid hormones in plasma (the dose of levothyroxine should be increased during pregnancy), and drugs that induce the metabolism of levothyroxine (rifampicin, barbiturates, carbamazepine, phenytoin) (6, 10, 11).

Ideally, the drug should be taken at least 30-60 min before breakfast, or at least 3 hours after the last daily meal, in order to achieve optimal absorption. It seems that acidic pH in the stomach, which is present under fasting conditions, may be important for levothyroxine absorption. Supporting this is the finding that the efficacy of levothyroxine might be decreased by proton pump inhibitors (10, 12). As an *in vitro* study has shown that coffee can sequester levothyroxine, this indicates that coffee reduces the absorption of levothyroxine (10, 13). The interaction appears to be avoided by taking levothyroxine with water and not drinking coffee for at least 60 minutes afterwards (12). Fe^{+2}, Al^{+3}, Mg^{+2} and Ca^{+2} ions can reduce levothyroxine resorption; it is necessary to separate the administration of preparations with these ions and levothyroxine by at least 4 hours. INR (International normalized ratio) monitoring is advised in patients on levothyroxine and warfarin/acenocoumarol, due to the risk of bleeding (10, 12, 14).

Serious side effects of levothyroxine rarely occur if the dosage is appropriate and if the patient is carefully monitored. An overdose of levothyroxine (iatrogenic thyrotoxicosis) can lead to the development of atrial fibrillation and osteoporosis.

Hypothyroidism in pregnancy

Hypothyroidism in pregnant women increases the risk of adverse gestational outcomes (miscarriage, preterm delivery), and may also have an adverse effect on the fetus (neuronal development). Levothyroxine replacement therapy in pregnancy is indicated for *clinical* and *subclinical* (asymptomatic or mild clinical manifestation, normal concentration of thyroid hormones, but slightly elevated TSH level) *hypothyroidism*. The following TSH reference ranges are recommended in pregnancy:

0.1-2.5 mIU/L in the first trimester; 0.2-3.0 mIU/L in the second trimester; 0.3-3.0 mIU/L in the third trimester. The level of total T_4 during the II and III trimesters should be 1.5 times higher than that of the general population due to the increase of thyroxine binding-globulin, affected by estrogen. If hypothyroidism existed before pregnancy, levothyroxine doses usually need to be increased by 25-50% during pregnancy, due to increased thyroxine binding-globulin, volume of distribution, and increased use of levothyroxine by the fetus (2, 6, 7, 8, 9).

Hyperthyroidism

Pathogenesis

Graves' disease (Basedow's disease), an autoimmune illness (a form of *primary hyperthyroidism*), is the most common cause of hyperthyroidism, in which thyroid stimulating antibodies (TRAb) bind to TSH receptors in the thyroid gland and mimic the action of prolonged TSH stimulation, resulting in increased synthesis and release of thyroid hormones.

Almost all patients with Graves' disease have TRAb in their serum and they are relatively specific for this disease (15-17).

Diagnosis of hyperthyroidism

The diagnosis of Graves' hyperthyroidism is made based on laboratory analyses (TSH in serum is decreased, FT_4 is increased above reference values, as well as TRAb); clinical manifestations (anxiety, tremor, irritability, fatigue, weakness, weight loss with increased appetite, diarrhea, eyelid retraction, palpitations, thyroid dermopathy); ultrasound of the thyroid gland, preferably with measurement of blood flow through the gland. If the clinical signs and symptoms and ultrasound of the thyroid gland are not clear enough, it is necessary to perform a radioactive iodine fixation test (3, 15-17).

Treatment of hyperthyroidism

Once a diagnosis of Graves' hyperthyroidism is made, the disease is treated by reducing thyroid hormone synthesis, using an antithyroid drug, or reducing the amount of thyroid tissue with radioiodine (^{131}I) treatment or by thyroidectomy. The main antithyroid drugs are *thioamides*. Thioamides are *propylthiouracil*, *thiamazole* (*methimazole*), and carbimazole (prodrug of *thiamazole*, not available in Serbia), and they are the drugs of choice in children, pregnant women and adults with milder forms of Graves' disease, with a low possibility of disease relapse, who are not candidates for surgery and application of ^{131}I. A high concentration of iodine, which decreases the synthesis and release of thyroid hormones, may also be used (2, 4, 15-17).

The main *mechanism of action* of thioamides is the inhibition of thyroperoxidase (TPO), which prevents the incorporation of iodine into tyrosyl residues of thyroglobulin, and the coupling of these iodotyrosyl residues to form iodothyronines. In addition to blocking hormone synthesis, propylthiouracil also partially inhibits the peripheral

conversion of T_4 to T_3, while this effect is less pronounced with thiamazole. This provides a rationale for the choice of propylthiouracil over other antithyroid drugs in the treatment of severe hyperthyroid states or of thyroid storm. These drugs also reduce thyroid antibody levels by a mechanism that is unclear, and they lead to long-term remission of the autoimmune process. During thioamide therapy, there is a drop in the concentration of antibodies directed towards the TSH receptor. The onset of action of these drugs is delayed, due to the large reserve of thyroid hormone precursors in the thyroid gland. Control of symptoms is usually achieved in one to two months, and the dose is titrated based on unbound T_4 levels. TSH levels often remain suppressed for several months and therefore do not provide a sensitive index of treatment response (1).

Adverse effects from thiourea antithyroid drugs occur most frequently during the first 8 weeks of treatment. The most common minor adverse effects are nausea, vomiting, gastric discomfort, headache, arthralgia, rashes and pruritus. These effects are usually self-limiting and may resolve spontaneously or after substitution with alternative antithyroid drug; rashes may respond to an antihistamine. Rare but major side effects include hepatitis (especially with propylthiouracil; avoid use in children) and cholestasis (thiamazole); vasculitis; and most importantly agranulocytosis (< 1%). It is essential that antithyroid drugs are stopped and not restarted if a patient develops major side effects. Patients should be told how to recognise such toxicity and should be advised to seek immediate medical attention if mouth ulcers, sore throat, fever and malaise develop. It is not useful to monitor blood counts prospectively, because the onset of agranulocytosis is idiosyncratic and abrupt. If there is a serious adverse reaction to one of the thioamides (agranulocytosis, hepatotoxicity), it should not be substituted with an alternative antithyroid drug, because there is cross-reactivity (1, 2, 15-17).

Thiamazole and propylthiouracil are equally effective in the treatment of Graves' disease, but in most cases preference should be given to thiamazole, due to its better tolerability and simpler dosing regimen (thiamazole is usually given twice-daily, but once-daily dosing is possible after euthyroidism is restored; propylthiouracil is usually given in 3-4 divided doses throughout the course). The use of propylthiouracil is reserved for women in the first trimester of pregnancy and in *thyroid storm* (life-threatening exacerbation of hyperthyroidism: fever, delirium, convulsions, vomiting, diarrhea, coma) (2, 3, 15-17).

Long-term remission with thioamides is achieved within 12-18 months in up to 50-60% of cases. Risk factors for disease relapse are male gender, smoking, large goiters, and a high titer of TRAb after completion of therapy, but outcomes are difficult to predict. Expectations that the probability of remission will be higher if high doses of thioamide and levothyroxine are combined (so-called *block-replace therapy*) have not been fulfilled, but this type of therapy is still used. When treatment stops, the FT_4 level should be monitored for 2-3 months during the first year. Patients who relapse after discontinuing thioamide therapy should be referred for surgical treatment or radioactive iodine therapy (1, 2, 3, 15-17).

Radioactive iodine therapy is a suitable approach for the treatment of Graves' disease in patients with comorbidities that preclude a surgical procedure, as well as for patients who have not responded to antithyroid drug therapy or who have relapsed after it. Patients with severe forms of active ophthalmopathy are not ideal candidates for radio iodine therapy, and preference should therefore be given to thioamides and surgery. The goal of ^{131}I administration is to control hyperthyroidism by bringing the patient into a euthyroid state. However, in a large number of cases, permanent hypothyroidism develops after the administration of ^{131}I, and it is necessary to initiate levothyroxine replacement therapy (1-4, 15-17).

Radio iodine therapy is an oral sodium iodide that emits both γ rays and β particles. ^{131}I is rapidly trapped by the thyroid, and deposited in the colloid of the follicles, from which it is slowly liberated. The destructive β particles almost exclusively treat the parenchymal cells of the gland, with little or no damage to surrounding tissue. The γ radiation passes through the tissue and can be quantified by external detection. With the appropriate dose of ^{131}I it is possible to destroy the thyroid gland completely without injury to adjacent tissue. Thiamazole has to be stopped 2-3 days before radioiodine administration to achieve optimum iodine uptake, and can be restarted 3-7 days after radioiodine in those at risk of complications from worsening thyrotoxicosis. Although it has been considered that a poor response to radioiodine is more likely with propylthiouracil than thiamazole, this has not been supported by meta-analysis (2).

Absolute contraindications for the use of radio iodine therapy in the treatment of Graves' disease are pregnancy, breastfeeding, thyroid cancer (or suspicion to cancer), as well as use in women who plan to become pregnant soon. Moreover, ^{131}I should not be used in patients with gastrointestinal disorders such as gastritis, peptic ulcer, dysphagia, and esophageal stricture (2, 15-17).

Side effects of ^{131}I are dry mouth (inflammation of the salivary glands) and eyes, gastrointestinal disorders and bone marrow suppression. The most significant complication is worsening of ophthalmopathy, especially in smokers (1, 2).

Propranolol is a drug of choice for control adrenergic symptoms, especially in the early stages before antithyroid drugs take effect. This β blocker treats palpitations, tremor, and anxiety. *Benzodiazepines* are also used to control anxiety (15-17).

Ophthalmopathy usually does not require treatment if it is mild to moderate, because in most cases it resolves spontaneously. Serious ophthalmopathy, with optic nerve damage and conjunctival edema, requires an urgent ophthalmological examination. Two-thirds of patients experience short-term improvement with high-dose glucocorticoids (eg, prednisone, 40-80 mg/day), which can be combined with mycophenolate sodium (Europe), or teprotumumab (US). If the patient does not respond well to glucocorticoid therapy, removal of part of the orbital (cheekbone) bone is resorted to (1, 2, 15-18).

Thyroid dermopathy usually does not require treatment, but it can cause cosmetic problems, or problems with wearing shoes. If necessary, glucocorticoid based ointments can be applied topically to the skin under an occlusive dressing (15-17).

Iodide is used preoperatively to stabilize the thyroid gland and reduce its vascularization. Iodide is used in thyrotoxic storm/crisis to reduce the release of thyroid hormones (1, 2).

Thyroid storm is associated with significant mortality and requires urgent treatment, which usually include: fluid replacement, large doses of propylthiouracil and iodide for the suppression of synthesis and release of thyroid hormones, propranolol, and hydrocortisone/dexamethasone (preventing adrenal insufficiency) (2, 15-17).

Conclusion

The most common cause of primary hypothyroidism is Hashimoto's thyroiditis. When the diagnosis of primary hypothyroidism is made, it is necessary to start substitution therapy with levothyroxine. The dose of levothyroxine depends on body weight, comorbidities and interactions with other drugs. On the other hand, the most common cause of thyrotoxicosis is Graves' disease. Different approaches can be used in the treatment of Graves' disease: antithyroid drugs (thiamazole and propylthiouracil), radioactive iodine and surgical procedure. Propranolol is important for alleviating the manifestations of thyrotoxicosis as well, and it is also used during radioactive iodine therapy and surgical procedures.

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Klinička farmakologija levotiroksina i antitiroidnih lekova

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Kratak sadržaj

Najčešća oboljenja štitaste žlezde su autoimune bolesti praćene razvojem hipotiroidizma (Hašimotov tiroiditis) i hipertiroidizma (Grejvsova bolest). Hipotiroidizam je klinički sindrom koji nastaje kao posledica deficita tiroidnih hormona. Hipertiroidizam je preterana aktivnost tiroidne žlezde praćena hipersekrecijom tiroidnih hormona. Pojednostavljeno, za postizanje eutiroidnog stanja u oba klinička sindroma se koriste (najčešće) dva leka – levotiroksin (hipotiroidizam) i tioamid (hipertiroidizam). Naizgled je jednostavno, ali zapravo tokom lečenja, koje je u slučaju hipotiroidizma doživotno, treba pažljivo pratiti pacijente uz prilagođavanje doze leka i uključivanje drugih lekova za lečenje komorbiditeta.

Ključne reči: Hašimotov tiroiditis, Grejvsova bolest, levotiroksin, tiamazol, propiltiouracil