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Recent Advances in Antithyroid Agents, A Review

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Abstract

Thyroid gland comprising of two lobes (right and left) is located in the neck region below Adams apple. The gland as such is responsible for secreting Triiodothyronine, Thyroxine and Calcitonin. The former two is responsible for various metabolic and developmental growth while the latter maintains calcium homeostasis. Hypothyroidism and Hyperthyroidism occurs when the level of circulating thyroid hormones is either insufficient or surplus to meet body requirement. Various drugs have been used to modulate the function of thyroid gland and prevent life threatening outcomes.

Keywords: Thyroid gland; Diseases; Triiodothyronine; Thyroxine; Calcitonin.

Introduction

Though the size of thyroid gland is butterfly shaped but its functionis way beyond that. Thyroid gland is located in the neck below the Adams apple whichcomprises of two connected lobes. The two lobes are connected by a thin sheet called isthmus. It has been reported that he gland increases in size during pregnancy and is larger in women than in men. The gland as a whole is formed by numerous thyroid follicles whichare the functional unit of thyroid gland. The follicular cells line the spherical thyroidfollicle with intermittent presence of parafollicular cells. As the shape of parafollicular cells is "C-Shaped" it is often referred as C cells of the thyroid gland.[1] Both follicular and parafollicular cells surrounds the lumen containing colloid. The follicular cells of the thyroid gland are responsible for secreting two main hormones Triiodothyronine (T3) and Thyroxine (T4) while the parafollicular cells secretes calcitonin hormone. The role of the thyroid hormone (T3 & T4) is to regulate the metabolic rateand protein synthesis in adults while regulation of growth and development in children is governed by the gland. Calcitonin plays a major role in maintaining calcium homeostasis. The whole process of thyroid hormone release is controlled by Hypothalamus. Whenever required, the hypothalamus releases Thyroid Releasing Hormone (TRH). This signal is received by the anterior pituitary and the latter releases Thyroid Stimulating Hormone (TSH). TSH then interacts with the follicular and parafollicular cells of thyroid gland and stimulate T3, T4 and Calcitonin release from the thyroid gland.[3] A number of other factors have been reported to influence thyroid hormone secretion. In rodents and children, exposure to a cold environment triggers TRH secretion, leading to enhanced thyroid hormone release. This shows the relationship of thyroid hormone with body heat regulation. This review sole discusses the drugs used of hyperthyroidism as treatment of hypothyroidism is often successfully achieved

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by supplying synthetic thyroid hormones readily available in the market.

Thyroid Hormones and Their Roles

The sole function of the thyroid gland is to produce two steroid hormone (T3 & T4) and one peptide hormone (Calcitonin). Iodinated tyrosine residue is the main ingredient for thyroid hormones.Per molecule of T3 and T4 are comprises of 3 atoms and 4 atoms of iodine respectively hence the name Triiodothyronine and Tetraiodothyronine.[4] In the body the thyroid hormones regulate mainly three function. These includes:

- Metabolic: Thyroid hormones influence metabolic activity by increasingthe basal metabolic rate. The hormones facilitate the breakdown, absorption and cellular uptake of glucose. They also stimulate the breakdown of fats, and increase the number of free fatty acids. Despite increasing free fatty acids, thyroid hormones decrease cholesterol levels, perhaps by increasing the rate of secretion of cholesterol in bile.[5]
- *Cardiovascular:* The rate and force of cardiac contraction is also influenced by the hormones. Both rate of breathing and oxygen consumption is increased byenhancing the activity of cell mitochondria. All these events Combined,increase blood flow and the body's temperature.
- *Developmental:* Thyroid hormones are important for normal development. They increase the growth rate in young ones, and cells of the developing brain are a major target for the thyroid hormones T3 and T4. Thyroid hormones play a crucial role in brain maturation during foetal development and first few years of postnatal life.
- Moreover, the thyroid hormones also play a role in maintaining normal sexual function, sleep, and thought patterns.

Only a fraction of thyroid hormone travel freely in the blood after its release from gland. Most are bound to thyroxine-binding globulin (TBG) and to a lesser extent to transthyretin, and albumin. The hormonal activity lies in only 0.03% of T4 and 0.3% of T3 traveling in the body in unbound form. In addition, up to 85% of the T3 in blood is produced following conversion from T4 by iodothyronine deiodinases in organs around the body.[6]

Once the hormone crosses the cell membrane it goes and binds to nuclear thyroid hormone receptors TR-α1, TR-α2, TR-β1 and TR-β2, the hormone receptor complex then bind with hormone response elements and transcription factors and modulate DNA transcription of the specific protein . Including all these role, thyroid hormones also interacts with enzymes like calcium ATPase and adenylyl cyclase, and glucose transporters[7] in the cell cytoplasm.

Table 1 (below) shows the Pharmacokinetic data of T4 and T3.

Table 1: Pharmacokinetic data of T4 and T3.

Variable	T_4	T_3
Volume of distribution	10 L	40 L
Extrathyroidal pool	800 mcg	54 mcg
Daily production	75 mcg	25 mcg
Fractional turnover per day	10%	60%
Metabolic clearance per day	1.1 L	24 L
Half-life (biologic)	7 days	1 day
Serum levels		
Total	4.8–10.4 mcg/dL	60–181 ng/dL
	(62–134 nmol/L)	(0.92–2.79 nmol/L)
Free	0.8–2.7 ng/dL	230–420 pg/dL
	(10.3–34.7 pmol/L)	(3.5–6.47 pmol/L)
Amount bound	99.96%	99.6%
Biologic potency	1	4
Oral absorption	70%	95%

Source: Bertram G. Katzung. Basic and Clinical Pharmacology. 14th Edition.

Mechanism of Hormone Production

The thyroid hormones are synthesized from thyroglobulin. This is a protein in the colloid in the follicular lumen that is originally created within the rough endoplasmic reticulum of follicular cells and then transported into the follicular lumen. Thyroglobulin contains 123 units of tyrosine, which reacts with iodine within the follicular lumen.[8]

Iodine is the crucial element for the production of the thyroid hormones. Iodine (I^0) travels in the blood as iodide (I^-), which is taken up into the follicular cells by a sodium-iodide symporter (NIS). This ion channel transports two sodium ions and an iodide ion across the cell membrane. With the help of another transporter, pendrin, Iodide then travels from within the cell into the lumen. In the follicular lumen, iodide is then oxidized to iodine. This makes it more reactive, and the iodine is attached to the active tyrosine units in thyroglobulin by the enzyme thyroid peroxidase.[9] These then used as precursors to form

Monoiodotyrosine (MIT), and Diiodotyrosine (DIT). When the Thyroid Stimulating Hormone stimulates the follicular cells, thyroglobulin is reabsorbed by the follicular cellsfrom the follicular lumen. The iodinated tyrosines are cleaved, forming the thyroid hormones T4, T3, DIT, MIT, and traces of reverse triiodothyronine (rT3). Two molecules of DIT are combined to form 4DIT (Thyroxine) and one molecule of MIT and two molecules of DIT are combined to form (Triiodothyronine). rT3 is believed to be metabolically inactive. T4 in the periphery is converted to T3 and RT3by deiodinase enzymes . This forms the major source of both RT3 (95%) and T3 (87%) in peripheral tissues.[10]

Drugs Modulating Thyroid Functions Potassium Iodide

Iodine as potassium salt is commonly used for retarding or slowing down the thyroid function. The role of Iodine on thyroid gland are many. One of the major roleis to inhibit hormone release from the thyroid gland.This occurs within hours after the drug administration. This effect may result from inhibition of thyroglobulin proteolysis (which is necessary for production/excocytosis of thyroid hormones) Apart from this, Iodine also interferes with the synthesis of thyroid hormones by inhibiting thyroidal peroxidase enzyme which ultimately suppresses the rate of thyroid hormone production. It has been noticed that the maximal effect of iodine on thyroid hormone concentration occurs even after 10 days of treatment. For this reason, Iodine therapy is typically given only for a few weeks because the thyroid gland will commonly "escape" from iodide block in 2-8 weeks.[11] The decreased level of iodine inside the thyroid follicle triggers down regulation of sodium-iodine symporter on the basolateral membrane of the follicular cell. This usually occurs within two to four weeks of continual exposure after which the thyroid hormone biosynthesis resumes in normal fashion. Iodine is given to patients with Graves' disease with the motive to inhibit organification (Iodination of thyroglobulin) in the thyroid gland

Indications

Graves' disease, goiter,toxic adenoma and thyroiditis. It is rarely used as sole therapy for hyperthyroidism. Also used prior to thyroid gland surgery to decrease the vascularity of the thyroid gland.

Contraindications

Iodide can cross placenta and can cause foetal goitre in pregnancy.

Side Effects

Patient undergoing Iodine therapy may show symptoms such as acnerashsmetallic taste in the mouth, swollen salivary glands, ulcerations of mucous membranes (sore mouth), conjunctivitis and rhinorrhea.[12]

Propylthiouracil (PTU)

Propylthiouracil is a thiourea antithyroid agent. It inhibits the synthesis of thyroxine and inhibits the peripheral conversion of thyroxine to tri-iodothyronine. It is used in the treatment of hyperthyroidism (Grave's disease). It blocks thyroid hormone synthesis by inhibiting the thyroid peroxidase thereby blocking iodine organification. PTU decreases thyroid hormone production. PTU also interferes with the conversion of T4 to T3, and, since T3 is more potent than T4, this also reduces the activity of thyroid hormones.[13]

Mechanism of action

In the cell membrane, Propylthiouracil binds to thyroid peroxidase and inhibits the conversion of iodide to iodine. This enzymeis responsible for converting iodide to iodine (via hydrogen peroxide as a cofactor) and also catalysis the incorporation of the resulting iodide molecule onto both the 3 and/or 5 positions of the phenol rings of tyrosine found in thyroglobulin. Thyroglobulin is degraded to produce thyroxine (T4) and tri-iodothyronine (T3), which are the main hormones produced by the thyroid gland.[14] Consequently,production of new thyroid hormones are blocked by propylthiouracil.

As propylthiouracil blocks synthesis of thyroid hormone and not its release, there is a lag period and hence onset of action is said to be delayed. This often takes 3-4 weeks before stores of T4 are depleted as the already present hormones in the circulation continues to show its action.[15]

Indications

Thyrotoxicosis (thyroid storm) (high doses must be used to treat thyroid storm). PTU is favoured over methimazole for this indication because of its effect to block T4 to T3 conversion in peripheral

circulation.

Side Effects

Common side effect of PTU administration is rash. Other side effects includeoedema, agranulocytosis usually reversible upon drug withdrawal, hepatitis (rare, but potentially fatal), cholestatic jaundice (more common with methimazole)

Pregnancy

Risk Category D. PTU can cross the placental barrier & cause foetal hypothyroidism.PTU is more strongly protein-bound compared to methimazole, and therefore PTU is preferred in pregnancy if either are indicated for treatment of maternal hyperthyroidism.[16]

Methimazole

Methimazole is a member of the class of imidazole group in which hydrogen atom is replaced by a methyl group attached to a nitrogen. It shows antithyroid activity by inhibiting the enzyme, thyroid peroxidase. Its potency has been reported to be 10 times greater than propylthiouracil (PTU). The activity of Methimazole lies in its ability to successfully block the enzyme thyroid peroxidaseto provides antithyroid activity. Upon administration, it prevents thyroid hormone synthesis by inhibiting the thyroid peroxidase-catalyzed reactions & blocking iodine organification (the major mechanism of action).[17] Its mechanism of action on the thyroid gland is the same as PTU, however methimazole does not effectively block peripheral deiodinase that converts T4 to T3.

Of all the antithyroid drugs available in the market, methimazole is regarded and is often forming a first line drug for prescribers. Methimazole has been found to elevate serum aminotransferase during therapy causing cirrhosis of liver.

Indications

Methimazole is indicated for the treatment of hyperthyroidism in patients with Graves' disease or toxic multinodular goitre for whom thyroidectomy or radioactive iodine therapy are not appropriate treatment options. Methimazole is also commonly prescribed for the slowing down or suppress hyperthyroid symptomsand in initial stage of thyroidectomy or radioactive iodine therapy. Apart, methimazole carries the above indications and is also indicated for the medical treatment of hyperthyroidism regardless of other available treatment options. Methimazole is the primary drug used to treat Grave's hyperthyroidism in non-pregnant patients. The mechanism of action of mechanism is same with propylthiouracil however it is often preferred due to its long half life hence once a day dosing.Just like propylthiouracil, methimazole require 3-8 weeks to make patient euthyroid because it blocks the synthesis of new thyroid hormone, and already formed T3 & T4 are not effected.[18]

Side Effects

Maculopapular rash is seen in 5% of treated patients, fever is another but less common side effects associated with methimazole therapy. Other rare side effects like agranulocytosis may sometimes observed. Although, agranulocytosis induced by methimazole is often reversible upon discontinuation of drug but when occurs it is severe and life threatening it is always advice to have bone marrow status monitor of the recipient. Hepatitis, Cholestatic jaundice and GI stress are other uncommon side effects.

Contraindications

Pregnancy & nursing mothers - methimazole is found in breast milk & is contraindicated in nursing mothers, can cause fetal harm (hypothyroidism) when administered to a pregnant woman. It belongs to Pregnancy Risk Category D. Congenital malformations are rarely observed with methimazole.

Radioactive I -131

Iodine 131 is readily available as Sodium salt. Radioactive Iodine I-therapy is a treatment for an overactive thyroid, a condition called hyperthyroidism. Grave disease is a common manifestation of hyperthyroidism. The gland is overall swollen or a part of the gland is swollen by forming nodules within the gland. The production of thyroid hormones is greatly increased. Other indication It is rapidly absorbed & is concentrated in the thyroid where it is incorporated into storage follicles. Once inside the follicular cells it emits beta rays to destroy the thyroid cells. The half life of beta rays is 8 days which makes it highly radioactive. It is frequently used but in smaller dose. The emitted

Beta particles act on parenchymal cells with little damage to surrounding tissue.[19]

Indications

Thyroid function test is conducted by its ability to uptake radioactive iodine. Also used for Graves disease unresponsive to other existing therapy. It is also indicated for Thyroid cancer.

Contraindications

Pregnancy or nursing mothers

Side Effects

Delayed hypothyroidism

Conclusion

Thyroid gland is located below the Adam's apple and is composed of two lobes, right and left joined together by isthmus. The gland has major role in regulating body metabolism, growth and development. Triiodothyronine, Tetraiodothyronine and Calcitonin are the hormones secreted by the gland. The latter one, Calcitonin helps in regulating blood calcium level. A number of drugs have been developed to counteract or mitigate the symptoms of hyperthyroidism. The drugs mainly act on the pathway of thyroid hormone synthesis. Methimazole and Prophythiouracil are the most commonly used antithyroid drugs in the market. While Potassium Iodide and Radioactive I -131are less commonly used.

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