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Review Article

Antithyroid

Shreya Ingle*[1], Sunil Gaikwad[2]

[1]*B. Pharm at Sandip Institute of Pharmaceuticals Sciences, Mahiravani Nashik Maharashtra 422213*
[2]*M. Pharm at Sandip Institute of Pharmaceuticals Sciences Mahiravani Nashik Maharashtra 422213.*

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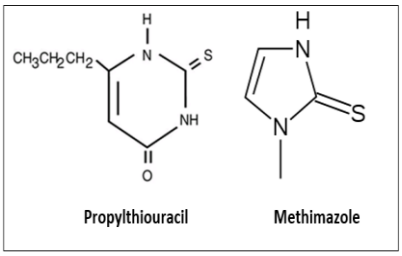
ABSTRACT

Thyroid hormones (THs) play key roles in modulating the overall metabolism of the body, protein synthesis, fat metabolism, neuronal and bone growth, and cardiovascular as well as renal functions. In this review, we discuss on the thyroid hormone synthesis and activation, thyroid hormone receptors (TRs) and mechanism of action, applications of thyroid hormone analogues, particularly the compounds that are selective ligands for TRβ receptors, or enzyme inhibitors for the treatment of thyroidal disorders with a specific focus on thyroid peroxidase and iodothyronine deiodinases. We also discuss on the development of small-molecule deiodinase mimetics and their mechanism of deiodination, as these compounds have the potential to regulate the thyroid hormone levels.

INTRODUCTION

Hyperthyroidism, a common thyroid disorder, refers to increased synthesis and secretion of thyroid hormones by the thyroid gland. Most common causes of hyperthyroidism are Graves' disease (GD), toxic multinodular goiter and toxic adenoma. There are three therapeutic choices for hyperthyroidism : thyroid surgery as the oldest modality, radioactive iodine (RAI) and antithyroid drugs (ATDs).



Propylthiouracil Methimazole

Thyroid disease is common and becomes more common with age. 5-9% of adults have subclinical thyroid disease, and 0.8-7.5% have thyroid disease. Thyroid hormone is the only biologically active substance containing iodine, which is known to have two important functions. They are

***Corresponding Author:** Shreya Ingle
Address: *B. Pharm at Sandip Institute of Pharmaceuticals Sciences, Mahiravani Nashik Maharashtra 422213.*
Email ✉: shreyaingle118@gmail.com,
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important determinants of normal development during animal and human development, especially in the central nervous system (CNS). In adults, thyroid hormones play a role in the regulation of metabolism in homeostasis and affect the functioning of almost all organs. The metabolism of thyroid hormone occurs primarily in the liver, but local metabolism also occurs in tissues such as the brain. In classical negative feedback, the amount of thyroid hormone is controlled by the pituitary hormone thyrotropin. The main effects of thyroid hormones are mediated by binding to the thyroid hormone receptor (TR) and regulating the transcription of specific genes. These receptors constitute the nuclear receptor superfamily. The thyroid gland secretes three hormones: thyroxine (T4), triiodothyronine (T3), and calcitonin. Subclinical thyroid disease is characterized by abnormal thyroid-stimulating hormone (TSH) but normal T4 and T3 levels and does not require treatment; patients with thyroid disease have abnormally mobile TSH, T4, and T3 levels that must be corrected. Known risk factors for thyroid disease include autoimmunity, external irradiation of the head and neck, defects in iodine tissue biosynthesis, tumor replacement of the thyroid gland, and use of certain medications. Other factors associated with the risk of thyroid disease include sex, age, and iodine deficiency. There are two major TR isoforms encoded on different genes: TRα and TRβ. TR binds to thyroid hormone response elements in the promoters of targets to regulate their transcription. TSH is a heterodimer composed of two subunits: TSHa and TSHβ. TSHα, known as the subunit of glycoprotein hormone α, is also a subunit of several other glycoprotein hormones such as LH, FSH, and human chorionic gonadotropin, while TSHβ is specific for TSH. T3 negatively regulates TSH by decreasing the TSHα and TSHβ genes and the transcription of the TRH gene. The major thyroid hormone in the brain is 3,5,3α-triiodothyronine (T3), which is derived primarily from the 5α deiodination of parent thyroxine (T4) by local brain deiodinases D2 and D3. Maternal T4 and T3 are transported from the mother's blood to the fetal brain across the blood-brain barrier. Hypothyroidism, in severe cases called myxedema, is the most common thyroid disorder. The disease is characterized by high levels of antibodies to thyroid peroxidase and, to a lesser extent, to thyroglobulin. In addition, blocking of antibodies to TSH receptors may also occur, which can lead to further adverse reactions. The failure of the thyroid gland to produce enough thyroid hormone is the most common cause of thyroid insufficiency, called primary hypothyroidism. Central hypothyroidism occurs rarely and is caused by a decrease in TSH in the thyroid gland due to insufficiency of the pituitary gland (secondary hypothyroidism) or the hypothalamus (tertiary hypothyroidism). Hypothyroidism present at birth (congenital hypothyroidism) is the most common mental retardation in the world. There are several treatment options for patients with hyperthyroidism, including the use of antithyroid drugs to reduce hormone synthesis and secretion, radioactive iodine administration, or surgical removal of the tumor. In general, the results of treatment for thyroid disease are quite satisfactory, and most patients can be cured or controlled. This enzyme catalyzes the oxidation of iodide, iodination of tyrosine residues in thyroglobulin, and the synthesis of iodotyrosine (monoiodotyrosine, MIT, and diiodotyrosine, DIT), producing thyromydine, tetraiodothyronine (T3), and thyroxine (Thyroxine). ATD also has anti-inflammatory properties, which may be part of its role in the treatment of Graves' hyperthyroidism. The term "thyrotoxicosis" also includes conditions not related to hyperthyroidism but related to the process of thyroid destruction or the administration of exogenous thyroid hormones.

Classification of different forms of thyrotoxicosis

With hyperthyroidism	Without hyprthyroidism
Common forms: Graves' disease, Toxic adenoma, Toxic multinodular goiter, Iodine-induced thyrotoxicosis. Uncommon forms: Congenital hyperthyroidism, Hashitoxicosis, TSH-secreting pituitary adenoma, Trophoblastic tumours, Metastatic thyroid carcinoma, Struma ovarii	*Common forms:* Sub-acute (De Quervain's thyroiditis), Painless thyroiditis, Post-partum thyroiditis, Iodine-induced thyrotoxicosis, Uncommon forms: Thyrotoxicosis factitia, Iatrogenic thyrotoxicosis**.**

Hyperthyroidism in pregnancy is a serious condition that increases the risk of adverse outcomes such as miscarriage, stillbirth, preterm birth, and fetal growth restriction. Management is difficult and is currently a major debate among endocrinologists. Antithyroid drugs (ATDs) have been used since the 1940s and are the treatment of choice during pregnancy. Radioactive iodine is strictly contraindicated, and thyroidectomy is more likely to occur during pregnancy than in nonpregnant women and may increase the risk of fetal thyrotoxicosis. A randomized controlled trial of measures in pregnant women with hyperthyroidism. However, carbimazole (CBZ) and its metabolites methimazole (MMI) and propylthiouracil (PTU) are both considered effective in the treatment of hyperthyroidism. Therefore, the choice of ATD is not based on relative therapeutic benefits, but on the risk of side effects and particularly serious consequences such as teratogenicity and severe pain. The aim of this review is to explore considerations regarding the choice of ATD used during pregnancy and when planning to become pregnant.

Vitamin D And the Thyroid –

Vitamin D is necessary for the normal functioning of many organs, including the thyroid gland. It is, therefore, not surprising that vitamin D deficiency is considered a risk factor for the development of many thyroid disorders, including autoimmune thyroid diseases and thyroid cancer. However, the interaction between vitamin D and thyroid function is still not fully understood.

- Vitamin D in Autoimmune Thyroid Diseases-

thyroid disease is characterized by the immune system of the thyroid gland. Vitamin D supplementation has been shown to be beneficial in animal models of Graves' disease and thyroiditis. In addition, a meta-analysis by Xu et al, which included 26 studies (1,748 Graves' disease and 1,848 controls), noted that patients with Graves' disease were more likely to have vitamin D deficiency. Vitamin D can regulate the function of many aspects of the immune system

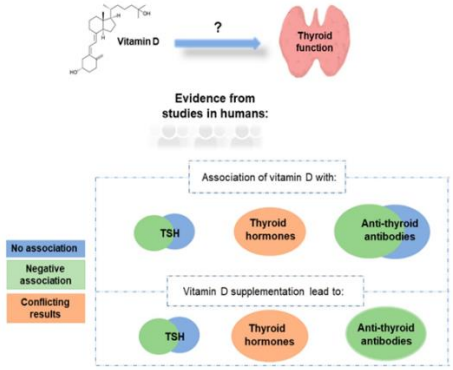
and participate in the regulation of the body. Vitamin D inhibits the production of proinflammatory cytokines such as IL-6, IL-8, IL-9, IL-12, IFN-γ, and TNF-α. It also increases the production of anti-inflammatory cytokines such as IL-10, IL-5 and IL-4. All the benefits of vitamin D are thought to be preventive. Although many studies have been conducted to show the role of vitamin D in the development of autoimmune thyroid diseases, it is still unclear whether vitamin D deficiency is a factor in the disease or a result of autoimmune thyroid disease.

- **Vitamin D in Thyroid Cancer-**

The incidence of thyroid cancer is increasing. In 2017, 255,490 new cases of cancer were diagnosed worldwide, compared to only 95,030 in 1990. The various types of thyroid cancer (papillary, Hurthle cell, and follicular thyroid cancer), benign thyroid cancer, and anaplastic thyroid cancer arise from follicular thyroid cancer cells. Medullary thyroid carcinoma results from malignant transformation of parafollicular neuroendocrine cells. The most common type of thyroid cancer is differentiated thyroid cancer, with papillary thyroid cancer accounting for 85% of cases. Vitamin D has been shown to be effective in cancer treatment by both in vitro and in vivo studies. In vitro studies have shown that calcitriol and its analog (MART-10) can inhibit the growth and metastatic potential of anaplastic thyroid cancer cells, respectively. In addition, the expression of VDR and other genes involved in vitamin D expression was increased in breast cancer cells, suggesting that vitamin D may play a tumor-protective role in cancer treatment. In vivo studies have shown that calcitriol treatment reduces tumor size in follicular thyroid cancer and metastatic follicular thyroid cancer mouse models.

The Effect Of Vitamin D On Secretion Of Tsh, Thyroid Hormones & Anti-Thyroid Antibodies-

Studies in healthy participants have generally shown variability or lack of correlation between TSH and 25(OH)D levels, and the same pattern has been observed in studies in cancer patients. Conflicting results have been found regarding thyroid hormones, with positive, negative, or no effects on 25(OH)D levels in healthy participants. Studies in patients with autoimmune thyroid disease are also controversial. Two-thirds of studies found no association, and one-third found an interaction between TSH and 25(OH)D levels. On the other hand, most studies in patients with autoimmune thyroid disease found no association between thyroid hormones and 25(OH)D levels. Regarding antithyroid antibodies, most studies found a positive correlation between antithyroid antibodies (antithyroid peroxidase antibody [TPOAb], antithyroglobulin antibody [TgAb], or TSH receptor antibody [TSHRAb]) and 25(OH)D levels, but many studies failed to assess this association.



Association of vitamin D with thyroid function

Symptoms Of Hyperthyroidism And Hypothyrodism-

Symptoms of Hypothyroidism (An underactive thyroid)-

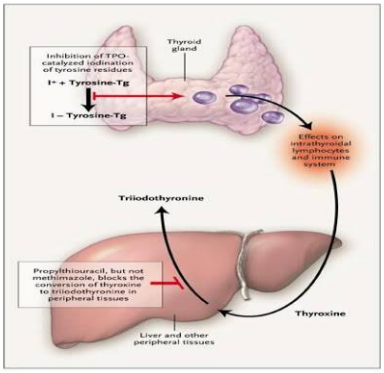
Fatigue; exhaustion feeling run down and sluggish depression, moodiness difficulty concentrating; brain fog;unexplained or excessive weight gain; dry, coarse and/or itchy skin; dry, coarse and/or thinning hair; feeling cold, especially in the extremities; constipation; muscle cramps; increased menstrual flow; more frequent periods; infertility/miscarriage; low blood pressure; frequent infections; bloating/puffiness in hands, feet, eye area, face, etc. *Symptoms of Hyperthyroidism (An overactive thyroid)-* Nervousness; irritability; increased perspiration;thinning of your skin; fine brittle hair; muscular weakness especially involving the upper arms and thighs; shaky hands; panic disorder; insomnia; racing heart; more frequent bowel movements; weight loss despite a good appetite; lighter flow, less frequent menstrual periods,etc.

Adverse Effects of Antithyroid Drugs-

Thyroid hormone, especially thyroxine, are widely used either at replacement doses to correct hypothyroidism or at suppressive doses to abolish thyrotropin (thyroid-stimulating hormone) secretion in patients with differentiated thyroid carcinoma after total thyroidectomy or with diffuse/ nodular nontoxic goitre. In order to suppress thyrotropin secretion, it is necessary to administer slightly supraphysiological doses of thyroxine. Possible adverse effects of this therapy include cardiovascular changes (shortening of systolic time intervals, increased frequency of atrial premature beats and, possibly, left ventricular hypertrophy) and bone changes (reduced bone density and bone mass), but the risk of these adverse effects can be minimised by carefully monitoring serum free thyroxine and free liothyronine (triiodothyronine) measurements and adjusting the dosage accordingly. Thionamides [thiamazole (methimazole), carbimazole, propylthiouracil] are the most widely used antithyroid drugs. They are given for long periods of time and cause adverse effects in 3 to 5% of patients. In most cases, adverse effects are minor and transient (e.g. skin rash, itching, mild leukopenia). The most dangerous effect is agranulocytosis, which occurs in 0.1 to 0.5% of patients. This life-threatening condition can now be effectively treated by granulocyte colony-stimulating factor administration. Other major adverse effects (aplastic anaemia, thrombocytopenia, lupus erythematous-like syndrome, and vasculitis) are exceedingly rare.

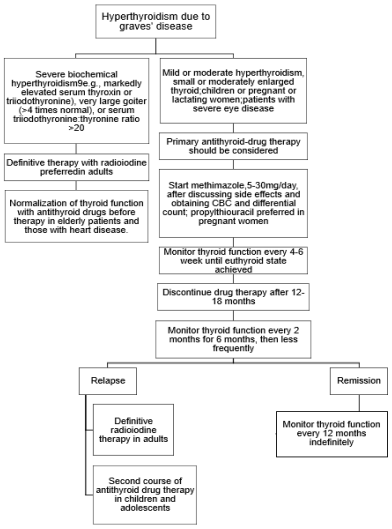
Effects Of Anti Thyroids Drugs-

Various effects of antithyroid drugs include inhibition of thyroid hormone synthesis and reduction of intrathyroidal immune dysregulation and (in the case of propylthiouracil) peripheral conversion of thyroxine to triiodothyronine. Tyrosine-Tg represents the tyrosine residue in thyroglobulin, I+ represents the iodinated environment, and TPO represents thyroid peroxidase.



Algorithm for the Use of Antithyroid Drugs among Patients with Graves' Disease-

Antithyroid medications are first-line treatment for adults with mild to moderate hyperthyroidism or goiter and are also a treatment for children, adolescents, and pregnant or breast-feeding women. Radioactive iodine may be more appropriate as a first-line treatment for adults in the United States, but it is not the case for adults in other parts of the world. Subtotal or near-total thyroidectomy is an option for some patients after antithyroid drug therapy. Radioactive iodine therapy is the preferred option for adults who relapse. Some patients prefer secondary thyroid medications, and this strategy is appropriate for children and adolescents. CBC stands for complete blood count.



The usual starting dose for methimazole is 15 to 30 mg once daily and for propylthiouracil is 300 mg daily in three doses. However, in many patients the disease can be controlled with small doses of methimazole, suggesting that the 10:1 acceptance ratio for methimazole compared with propylthiouracil is an underestimate. In later analyses, very severe methimazole can cause mild hyperthyroidism in patients. Annual monitoring of thyroid function for six weeks is recommended, at least until thyroid function is stable or the patient is euthyroid. After 4 to 12 weeks, most patients have improved thyroid function or have reached euthyroid function, at which time the drug can usually be tapered while maintaining thyroid function. In many patients the disease can be controlled with a low dose of methimazole, 5 to 10 mg daily or propylthiouracil, 100 to 200 mg. In fact, if the dose is not reduced appropriately, hypothyroidism or goiter may occur. After the first three to six months, the interval may be increased to every two to three months, then to every four to six months. Despite normalization of thyroid hormones, the level of thyrotropin in the blood remains unchanged for weeks or months, so measuring thyrotropin is not an early measurement. In addition, patients may sometimes have elevated serum triiodothyronine levels despite normal or even low thyroxine or free thyroxine levels, indicating that antithyroid drugs should be increased rather than reduced.

Antithyroid Activity of Herbal Plants-

Some plants isoflavonoids have profound effects on thyroid hormones and on the hypothalamus–pituitary axis. Genistein and daidzein from soy (Glycine max) inhibit thyroperoxidase that catalyses iodination and thyroid hormone biosynthesis. Other plants with hypothyroid effects include pearl millet (Pennisetum glaucum) and fonio millet (Digitaria exilis); thiocyanate is

found in Brassicae plants including cabbage, cauliflower, kale, rutabaga, and kohlrabi, as well as in tropical plants such as cassava, lima beans, linseed, bamboo shoots, and sweet potatoes. Tobacco smoke is also a source of thiocyanate.

The antithyroid and goitrogenic effects of Brassicae plants (Family Cruciferae) have long been known including cabbage (Brassica oleracea), broccoli, cauliflower, kale, kohlrabi, Brussels sprouts, and rutabaga (swede or yellow turnip, Brassica napobrassica), rapeseed and mustard. SCN interferes with active uptake and concentration of inorganic iodide by the thyroid and inhibits the enzyme thyroperoxidase thereby preventing the incorporation of iodine into thyroglobulin. Rutabaga and turnips contain a thiourea like product (progoitrin), a precursor of goitrin that also interferes with thyroperoxidase.

The most useful herbal remedies for both under and overactive thyroid are sea plants. Bladder wrack, a form of kelp, is used in both western and Chinese herbal medicine. It can be taken as a supplement or as an infusion. Pour boiling water over 2 to 3 tsp. of the dried herb and steep for 10 minutes. This remedy is useful if there is a deficiency of iodine in the diet. Bitters are helpful for mild cases of hypothyroidism. These can be found in natural foods stores usually as a liquid supplement. Hyperthyroidism can be supported by an herb called bugleweed. This herb should not be taken without a doctor's support. It can interfere with thyroid replacement therapy, should not be taken by pregnant women, and can result in enlargement of the thyroid. Insomnia associated with hyperthyroidism can be helped by valerian and passion flower. To use these herbs, take 15 drops of each tincture in water, one half hour before bed. Many more like botanical name of herbal thyroid stimulant, Gum guggle is commiphora mukul. The yellow resinous extract derived from the stem part of Mukul myrrh tree consists of volatile oils and resins in abundance. The pungent smell and acrid taste of this herb. The active compound in Guggle is called guggulsterone and has the power to influence thyroid function and improve the condition of hypothyroidism. A published journal titled 'Phototherapy research 'confirms the role of guggulsterone. An added advantage of having the herb is a decrease in the level of harmful cholesterol, one of the features of hypothyroidism. The incidence of side effect is low, but can range from headache, gastric upset, skin rash and rarely, hiccups.

Side Effects-

Antithyroid drugs can cause a variety of minor side effects as well as life-threatening and even fatal problems. The side effects of methimazole are dose-dependent, whereas the side effects of propylthiouracil are not significant. For patients with moderate hyperthyroidism, this may suggest a lower dose of methimazole instead of propylthiouracil. Agranulocytosis is the most concerning side effect of antithyroid drugs. In the largest series, agranulocytosis (absolute granulocyte count less than 500 cells per cubic millimeter) occurred in 0.37% of patients treated with propylthiouracil and 0.35% of patients treated with methimazole. Other rare side effects of antithyroid drugs are listed i.e,

Side effect	Estimated Frequency	Comments
Minor		
Skin reactions	4-6 %	Urticarial or macular reactions
Arthralgias	1-5 %	May be harbinger of more severe arthritis

Abnormal sense of taste or smell	1-5 %	Includes gastric distress and nausea
Sialadenitis	Rare	With methimazole only
Major		
Polyarthritis	1-2 %	So-called antithyroid arthritis syndrome
ANCA- positive vasculitis	Rare	ANCA positivity is seen in patients with untreated graves' disease and in asymptomatic persons who taking antithyroid drugs, especially propylthiouracil.
Agranulocytosis	0.1-0.5 %	Mild granulocytopenia may be seen in patients with graves' disease; may be more common with propylthiouracil.
Other hematologic side effects	Very rare	May include thrombocytopenia and aplastic anemia.
Immunoallergic hepatitis	0.1-0.2 %; 1 % in some series.	Almost exclusively in patients taking propylthiouracil; a transient increase in aminotransferase levels is seen in 30% of patients taking propylthiouracil.
Cholestasis	Rare	Exclusively with methimazole and carbimazole.
Hypoprothrombinemia	Rare	No case reports since 1982, only with propylthiouracil
Hypoglycemia	Rare	So-called insulin-autoimmune syndrome, which

		is seen mainly in Asian patients receiving sulfhy-dryl-containing drugs; only with methimazole.
Pancreatitis	Very rare	Once case report.

Skin Reactions-

Rash, urticaria, and minor allergic skin reactions such as hives are the worst side effects and usually occur within the first few weeks of treatment. In a meta-analysis of 5,136 patients, 6% of MMI users and 3% of PTU users reported rash, while 2% to 3% of patients had pruritus but no rash. In another randomized trial, skin reactions were described in 22% and 6% of patients treated with 30 mg MMI and 15 mg MMI, respectively. Approximately one-third of patients switched to another ATD after experiencing mild drug reactions and adverse events. Current ATA guidelines recommend antihistamine therapy without discontinuation of the ATD in patients with mild skin reactions, continuation or modification of the ATD in patients with moderate reactions, and avoidance of all ATDs in patients with more severe skin conditions. The median time from onset of skin reactions is approximately 20 days. Time to Onset of Complications After the Initiation of Antithyroid Drugs.

Complications	Time To Onset (Median)
Skin Reactions	20 Days
Hepatotoxicity	30 Days
Agranulocytosis	50 Days
Vasculitis	3.5 Years

Agranulocytosis-

Agranulocytosis is generally defined as a granulocyte matter of <500/mm3, but in most cases of ATD-associated agranulocytosis this fee reaches 0. The frequency of agranulocytosis is about zero.2%–0.5% (seventy eight), usually takes place in the first ninety days of remedy, and is dose-associated. Agranulocytosis may additionally arise after restarting the drug, although the drug has been used competently for a long term. signs include fever, malaise, and the onset of pharyngitis. a few research show a slow lower within the granulocyte matter, so monitoring of the white blood count number may additionally are expecting agranulocytosis. remedy of ATD-brought about agranulocytosis normally includes discontinuation of the drug, supplementation, administration of granulocyte colony-stimulating aspect, and wide-spectrum antibiotics. the general public of agranulocytosis takes place in the first 3 months of therapy

Hepatotoxicity-

ATD-induced hepatotoxicity ranges from mild transaminase elevation to fatal hepatic necrosis. In the United States, 1 to 3 liver transplants associated with PTU are reported to the FDA each year (1990 through 2007). Hepatotoxicity was reported in 0.3% and 0.15% of patients exposed MMI and PTU, respectively. Noninfectious liver disease was significantly higher in the MMI group than in the PTU group (0.25% vs. 0.08%). In contrast, patients with PTU had higher rates of morbidity than patients with MMI. The incidence of cholestasis was similar with both drugs. A

second study from China (80) reported that in 90 patients with severe hepatotoxicity
due to ATD, the majority of severe hepatotoxicity (81%) occurred within 12 weeks of PIA. The mean dose of MMI and PTU is approximately 20 mg and 200 mg, respectively, and the pattern of hepatotoxicity (cholestasis and hepatocellular damage) is similar for both drugs. Most hepatotoxicity occurs within the first 3 months of treatment.

Vasculitis-

Lupus erythematosus caused by ATD was first de scribed in 1970. Compared with other rare cases of ATD, it usually occurs after many years of trea tment. Surprisingly, patients with GD and those who remain asymptomatic while receiving ATD may be ANCA positive in the absence of ATD. R outine screening for ANCA positivity is not reco mmended. The usual presentation is fever, malais e, and joint pain. Patients may have clinical signs of cutaneous, pulmonary, and renal vasculitis inv olvement. Symptoms usually improve after regula r drug therapy, but some patients require antidiarr heal therapy and hemodialysis.

Arthralgias/ Arthritis-

Joint pain occasionally occurs during ATD treatment. Arthritis was reported in 1.6% of patients treated with ATD. These patients had joint pain in the hands, shoulders, hips, knees, or ankles and required general anesthesia for 1 to 3 weeks to control the pain. Joint swelling and erythema were rare.

Thyroid Hormones And Their Roles-

The role 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. In the body the thyroid hormones regulate mainly three function. These includes:

- **Metabolic**: Thyroid hormones influence metabolic activity by increasing the 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.
- **Cardiovascular**: The rate and force of cardiac contraction is also influenced by the hormones. Both rate of breathing and oxygen consumption is increased by enhancing the activity of cell mitochondria. All these events combined, increase blood flow and the body's temperature.
- **Development**: 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 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 and0.3% 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. 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 enzyme like calcium ATPase and adenylyl cyclase, and glucose transprters in the cell cytoplasm.

The pharmacokinetic data of T4 and T3.

Varaible	T4	T3
Volume of distribution	10 L	40 L
Extrathyroidal pool	800 mcg	54 mcg
Daily production	75 mcg	25 mcg
1. Fractional turnover per day.	10 %	60 %
Metabolic clearance per day	1.1 L	24 L
Half-life (biologic)	7 days	1 days
Serum levels Total	4.8-10.4 mcg / dL (62-134 nmol / L)	60-181 ng / dL (0.92-2.79 nmol / L)
Free	0.8-2.7 ng / Dl (10.3-34.7 pmol / L)	230-420 pg / dL (3.5-6.47 pmol / L)
Amount bound	99.96 %	99.6 %
Biologic potency	1	4
Oral absorption	70 %	95 %

Drugs Modulating Thyroid Function

Potassium Iodide-

Iodine as a potassium salt is often used to delay or slow thyroid function. The effects of iodine on the thyroid gland are numerous. One of its main effects is to inhibit the release of hormones from the thyroid gland. This occurs within a few hours of administration. This effect may be due to inhibition of thyroglobulin proteolysis, which is necessary for thyroid hormone production/exocytosis. Interference with thyroid hormone synthesis, resulting in inhibition of the rate of thyroid hormone production.

It has been noted that iodine still has the best effect on thyroid hormone levels even after 10 days of treatment. Therefore, iodine treatment is usually continued for only a few weeks, since the thyroid gland is usually "removed" by iodide blockade within 2-8 weeks. The decrease in iodine concentration in thyroid follicles leads to downregulation of the sodium-iodine symporter in the basolateral membrane of the follicular cells. This usually occurs within 2-4 weeks of persistent exposure, after which thyroid hormone biosynthesis returns to normal. .

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 goiter in pregnancy.

Side Effects-

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

Propylthiouracil (PTU)-

Propylthiouracil is a thiourea antithyroid agent. It inhibits the synthesis of thyroxine and inhibits the peripheral conversion of thyroxine to tri-iodoyhyronine. It is used in treatment of hyperthyroidism. It blocks thyroid hormones synthesis by inhibiting the thyroid peroxidase thereby blocking iodine organification. PTU decrease 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 acitivity of thyroid hormones**.**

Mechanism Of Action-

In the cell membrane, propylthiouracil binds to thyroid peroxidase and inhibits the conversion of iodide to iodine. This enzyme is responsible for converting iodide to iodine (via hydrogen peroxide as a cofactor) and also catalyst is the incorporation of the resulting iodide molecules 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 tri0iodothyronine (T3), which are main hormones produced by the thyroid gland. 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 taken 3-4 weeks before stores of T4 are depleted as the already present hormones in the circulation continues to show its action**.**

Indications-

Thyrotoxicosis (thyroid storm) (high doses must be used to treat thyroid storm). PTU is favoured over methimazole for this indication beacuase 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 include oedema, 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**.**

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 abilityto successfully block the enzyme thyroid peroxidase to 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). Its mechanism of action on 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 goiter for whom thyroidectomy or radioactive iodine therapy are not appropriate treatment options. Methimazole is also commonly prescribed for the slowing down or suppress hyperthyroid symptom sand in initial stage of thyroidectomy or radioactive iodine therapy. Methimazole is the primary drug used to treat Graves' hyperthyroidism in non-pregnant patients. The mechamism 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 PTU, methimazole require 3-8 weeks to make patirent euthyroid because it blocks the synthesis of new thyroid hormone, and already formed T3 & T4 are not effected.

side effects-

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

Contraindications-

Pregnancy & nursing mothers- methimazole is found in breast milk & its contraindicated in nursing mothers, can cause fetal harm (hypothyroidism) when administered to a pregnant woman. It belongs to Pregnancy Risk Category D. Congential 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. Graves' disease is 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 is rapidly absorbed & is concentrated in the thyroid where its 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.

Indications-

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

Contraindications-

Pregnancy or nursing mothers

Side Effects-

Delayed hypothyroidism.

Use Of Antithyroid Drugs During Pregnancy And Lactation-

Thyrotoxicosis occurs in 1 of every one thousand to 2000 pregnancies. due to its relative rarity, there aren't any potential medical trials evaluating drug regimens. despite the fact that, an antithyroid drug have to be commenced on the time of diagnosis, on account that thyrotoxicosis itself offers a hazard to the mother and fetus. Propylthiouracil has been preferred in North america because it became reputed to go the placenta minimally in comparison with methimazole. however, recent studies endorse that propylthiouracil does, in fact, pass the placenta,114,a hundred and fifteen and clinical records do not show any variations in thyroid feature at delivery among fetuses exposed to propylthiouracil as compared with those uncovered to methimazole. In North the united states, propylthiouracil remains the treatment of

desire throughout pregnancy, due to the fact congenital anomalies had been pronounced with methimazole, especially aplasia cutis, typically described as single or a couple of lesions of zero.5 to three cm on the vertex or occipital region of the scalp. This anomaly takes place spontaneously in 1 of 2000 births, however the frequency of this incidence in association with methimazole use isn't regarded. The usage of methimazole is also related to a totally rare teratogenic syndrome termed "methimazole embryopathy," which is characterized by choanal or esophageal atresia.119 In a current record, these anomalies took place in 2 of 241 children of girls exposed to methimazole, as compared with the spontaneous fee of 1 in 2500 to one in 10,000 for esophageal atresia and choanal atresia, respectively. because of the dearth of availability of propylthiouracil in many countries, methimazole (or carbimazole) continues to be broadly used in being pregnant. however,pregnant ladies need to be treated with propylthiouracil whilst the drug is to be had. inside the occasion of allergic reaction to propylthiouracil, methimazole may be substituted. The food and Drug management has classified each propylthiouracil and methimazole as elegance D agents (i.e., capsules with sturdy evidence of chance to the fetus) due to the potential for fetal hypothyroidism. Once the thyrotoxicosis has come underneath manage, the dose of antithyroid drug must be minimized to save you fetal hypothyroidism. If the maternal free thyroxine serum degree is maintained at or slightly above the higher restrict of everyday, the danger of fetal hypothyroidism is negligible.122 even supposing fetal thyroid consequences do arise, they're likely to be moderate,and observe-up studies of youngsters uncovered in utero have now not shown developmental or highbrow impairment. by using the 1/3 trimester, about 30 percentage of girls can discontinue anti-thyroid-drug therapy altogether and nonetheless stay euthyroid. For nursing moms, both antithyroid pills are considered safe. both seem in breast milk (methimazole greater than propylthiouracil)113 but in low concentrations. scientific studies of breast-fed in-fants have proven regular thyroid characteristic and everyday next highbrow development in exposed babies. each pills are authorized for nursing moms by way of the american Academy of Pediatrics.

Thyroid Strom-

Treatment of thyroid storm (sudden and dangerous onset of signs and symptoms of thyrotoxicosis) is beyond the scope of this review. However, antithyroid drug therapy plays an important role in the treatment of this condition. Although propylthiouracil is always preferred because of its effect on the conversion of thyroxine to triiodothyronine, there is no evidence that it is more effective than methimazole. A higher dose should be used, for example 60 to 120 mg methimazole or 600 to 1200 mg propylthiouracil per day (both drugs in divided doses). Both drugs can be administered rectally if necessary, and there is information that methimazole can be injected.

CONCLUSION

The thyroid gland is located under the Adam's fluid and has two lobes, the left and right, connected by the isthmus. These glands play an important role in regulating the body's metabolism, growth, and development. Triiodothyronine, tetraiodothyronine, and calcitonin are hormones secreted by tumors. Finally, calcitonin helps regulate calcium levels in the blood. Many medications have been developed to prevent or reduce the symptoms of hyperthyroidism. These drugs often act on the thyroid hormone synthesis pathway. Methimazole and propylthiouracil are the most commonly used antithyroid drugs on the market. Although potassium iodide and radioactive I-131 are rarely used. Over the last eight years, thioureas have been shown to be effective and even safe in the treatment of hyperthyroidism, especially GD in

children and adults. Of the two available ATDs, MMI is the drug of choice in most cases. PTU is commonly used in the first few months of pregnancy and in early pregnancy, in thyroid storm, and in patients with drug of choice in most cases. PTU is commonly used in the first few months of pregnancy and in early pregnancy, in thyroid storm, and in patients with children and adults. Of the two available ATDs, MMI is the of hyperthyroidism, especially GD in treatment hormones secreted by tumors. Finally, calcitonin helps regulate calcium levels in the blood. Many medications have been developed to prevent or reduce the symptoms of hyperthyroidism. These drugs often act on the thyroid hormone synthesis pathway. Methimazole and propylthiouracil are the most commonly used antithyroid drugs on the market. Although potassium iodide and radioactive I-131 are rarely used. Over the last eight years, thioureas have been shown to be effective and even safe in the hormones secreted by tumors. Finally, calcitonin helps regulate calcium levels in the blood. Many medications have been developed to prevent or reduce the symptoms of hyperthyroidism. These drugs often act on the thyroid hormone synthesis pathway. Methimazole and propylthiouracil are the most commonly used antithyroid drugs on the market. Although potassium iodide and radioactive I-131 are rarely used. Over the last eight years, thioureas have been shown to be effective and even safe in the treatment of hyperthyroidism, especially GD in children and adults. Of the two available ATDs, MMI is the drug of choice in most cases. PTU is commonly used in the first few months of pregnancy and in early pregnancy, in thyroid storm, and in patients with adverse side effects to MMI. ATD may be safely considered in the setting of Graves' orbitopathy. Recent studies have confirmed the efficacy and safety of long-term MMI in the treatment of GD and TMNG. The most common side effects of thioureas are mild skin reactions; despite the long history of ATD use, controversy continues regarding the chemistry and the different mechanisms of action. Immunomodulatory effects, adverse reaction process and predisposing conditions. Alternative thyroid therapy offers more information on improving lifestyle and nutrition, providing mental stimulation with natural thyroid supplements and prioritizing other body performance to improve thyroid function.

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