A review of drugs acting on the thyroid gland

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Abstract
Disorders of the thyroid gland are frequently encountered in the clinical practice setting. Typically, they fall into one of two categories: hypothyroidism, i.e. deficient levels of circulating thyroid hormone, or hyperthyroidism (or thyrotoxicosis) that involves abnormally high levels of thyroid hormone in the bloodstream. This article provides a high-level overview of thyroid function, the two major pathophysiological abnormalities of the thyroid gland, as well as treatment modalities aimed at managing patients with thyroid pathology.

Introduction
The thyroid gland forms part of the peripheral endocrine system, i.e. endocrine glands that are situated outside of the central nervous system. It is characteristically shaped like a bowtie (or butterfly). The central isthmus joins together its two lateral lobes. It is situated in the midline, anterior to the larynx and trachea, and at the level of the C5 to T1 vertebrae. The highly vascular thyroid gland secretes two blood-borne thyroid hormones that regulate the rate of the body’s basal metabolism, including energy levels and body temperature, as well as calcitonin that opposes the net effect of parathyroid hormone on plasma calcium levels in the regulation of calcium metabolism. The thyroid hormones also play a vital role in normal growth and development, and are able to augment the functions and effects of the sympathetic nervous system.

The two thyroid hormones which are secreted by the follicular cells are triiodothyronine (T₃) and thyroxine (tetraiodothyronine or T₄), which are both synthesised from tyrosine and iodine. Tyrosine is a nonessential amino acid that is synthesised in the body, and the iodine is derived from the diet. In the body, the negatively charged iodide ions are actively transported from the bloodstream into the follicular cells against a steep concentration (electrochemical) gradient by the sodium-iodide-symporter.

Approximately 90% of the secreted T₄ is converted to T₃ in peripheral target tissues outside of the thyroid gland. This process of activation mainly takes place in the liver and kidneys. T₃ is significantly more potent than T₄. Thyroid hormone secretion is regulated via the hypothalamic-pituitary-thyroid gland axis. Thyroid-stimulating hormone (TSH) from the anterior pituitary gland regulates the secretion of T₃ and T₄ into the bloodstream. In turn, TSH secretion is regulated by thyroid-releasing hormone (TRH) from the hypothalamus. Both T₃ and T₄ are capable of exerting negative or inhibitory feedback upon the release of TRH and TSH (Figure 1).

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Figure 1: Simplified diagram of the hypothalamic-pituitary-thyroid gland axis

(T₃): positive or stimulatory effect, (T₄): negative or inhibitory effect
T₃: triiodothyronine, T₄: thyroxine, TRH: thyroid-releasing hormone, TSH: thyroid-stimulating hormone

Note: Increased peripheral thyroid hormone levels will result in negative feedback to the anterior pituitary gland and hypothalamus. However, when these thyroid hormone levels are too low, the secretion of TRH and TSH will be increased accordingly.
Abnormal secretion of the thyroid hormones

There are two main categories of abnormal thyroid gland functioning: hypothyroidism, i.e. insufficient thyroid hormone secretion, and hyperthyroidism, i.e. excessive secretion of the thyroid hormones.

Hypothyroidism

Hypothyroidism refers to low plasma levels of the thyroid hormones because of inadequate production or secretion thereof by the thyroid gland. Inadequate levels of circulating thyroid hormone during foetal development and early infancy can result in a condition known as cretinism.

Three underlying mechanisms may result in the hyposecretion of thyroid hormone:

• An inadequate dietary intake of iodine, which is probably the most common cause of hypothyroidism worldwide.
• A secondary insufficiency because of deficient levels of TRH and/or TSH.
• As a result of primary gland failure of the thyroid itself.1,5

Hyperthyroidism

The condition is also referred to as thyrotoxicosis and is the result of excessive or hypersecretion of the thyroid hormone. Hyperthyroidism is usually caused by an autoimmune condition known as Graves' disease.

The other two causative mechanisms of hyperthyroidism are:

• Thyroid tumours that secrete excessive amounts of the thyroid hormone.
• A secondary excess because of abnormally high levels of TRH or TSH.1,5

Laboratory diagnosis of thyroid disorders

Thyroid function tests may be performed. Typically, these will include the levels of TSH, free T4, as well as T3 in the bloodstream. The levels of T3 and T4 will be low in hypothyroidism, with a compensatory increase in the level of TSH. The reverse is found in thyrotoxicosis, where the TSH level will be decreased, and the free levels of the thyroid hormones conversely increased.1,5

Pharmacology of thyroid drugs

Drug therapy used in the management of thyroid conditions has been utilised for more than a century. Anti-thyroid drugs are used in the management of hyperthyroidism, while drugs that are given to restore normal thyroid hormone concentrations in body tissue are employed to manage hypothyroidism. The latter aims to provide symptomatic relief and to prevent neurological deficits, i.e. cretinism, in newborn babies, as well as to reverse the biochemical abnormalities that are associated with hypothyroidism.6

Nonpharmacological management

Nonpharmacological measures can also be used in the management of hypo- and hyperthyroidism. Hyperthyroidism may either be managed by conservative treatment, i.e. antithyroid drugs, or by a reduction or ablation of the thyroid tissue, e.g. radioactive iodine and thyroidectomy.7

The surgical removal of the hypersecreting thyroid gland is a treatment option in patients with clinical symptoms which include:8

• A large thyroid (> 80 g).
• Severe ophthalmopathy.
• A decreased response to antithyroid drugs.

Following a thyroidectomy, hyperthyroidism may be persistent post surgery in 0.6-17.9% of patients suffering from Graves' disease, and especially in children. Complications of surgery frequently include hypothyroidism, while hypoparathyroidism and vocal cord abnormalities are less common.5,8

Table 1: Overview of the management of hypothyroidism

<table>
<thead>
<tr>
<th>Symptomatic hypothyroidism</th>
<th>Subclinical</th>
<th>Symptomatic hypothyroidism with normal TSH levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Symptomatic.</td>
<td>• TSH between 5 and 10 mU/L (free serum thyroxine in reference range).</td>
<td>• Check for alternate diagnosis.</td>
</tr>
<tr>
<td>• TSH levels of &gt;10 mU/L.</td>
<td>• Routine medicine management is controversial.</td>
<td>• Treat accordingly.</td>
</tr>
<tr>
<td>• Treatment with levothyroxine is most probably lifelong.</td>
<td>• Levels should be confirmed after 3-6 months and management re-assessed.</td>
<td>• Test dosages of levothyroxine may be initiated.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• This may assist in making a diagnosis.</td>
</tr>
</tbody>
</table>

TSH: thyroid-stimulating hormone
Management of hypothyroidism depends on the levels of TSH and the presenting symptoms of the patient. Table I provides an overview of the management of hypothyroidism.9

Pharmacological management

Hyperthyroidism

Methimazole, carbimazole, and propylthiouracil (PTU) are relatively simple molecules known as thionamides, and contain a sulphhydryl group and a thiourea moiety within a heterocyclic structure. These drugs are also the mainstay of antithyroid drug therapy.6,7,10 Collectively, they are referred to as the antithyroid drugs (ATDs). Their main mechanism of action is through the blockade of thyroid hormone synthesis by inhibition of thyroid peroxidase. This enzyme catalyses iodide oxidation, iodination of tyrosine residues onto thyroglobulin, and coupling of the iodotyrosines (monoiodotyrosine and diiodotyrosine) to form the thyronines, tetraiodothyronine or T4, and T3. An additional effect of PTU is to inhibit monodeiodination of T4 to T3.6,7,10 They also have immunosuppressive actions, which are useful in the management of Graves’ disease.

Antithyroid drugs are used in two ways:6
• The primary treatment for hyperthyroidism.
• Used in preoperative preparation before radiotherapy or surgery.

The following conditions may be managed with antithyroid drugs: Graves’ disease, toxic adenoma and toxic multinodular goitre. In the case of the last two, ATDs are used as a tool to prepare the patient for more definitive treatment. Antithyroid drugs are used as the primary treatment option in pregnant patients, as well as in children and adolescents.7,10

When prescribed for Graves’ hyperthyroidism, these drugs are used to induce a remission, defined as having normal thyroid hormone levels for one year after drug treatment has been stopped.7,10

In the management of hyperthyroidism, and when patients are fully compliant with the prescribed medicines, the ATDs may be highly effective. The choice of drug to be used is based on the decision that is made by the prescriber and the patient. However, methimazole has the advantage of a once-daily dosing regimen and serum T4 and T3 levels decrease more rapidly in patients who are treated with this drug. The risk of agranulocytosis is also lower with methimazole, and when used in moderate dosages, may improve compliance. This makes methimazole preferable to PTU.6,11

Once a patient has been started on treatment with an ATD, follow-up testing of thyroid function should be undertaken every 4-6 weeks until the thyroid function is stable, or until the patient is diagnosed as being euthyroid, i.e. having a normal thyroid function. Clinically, most patients improve considerably after 4-12 weeks. Drug dosing may be reduced to maintain a normal thyroid

<table>
<thead>
<tr>
<th>Body system</th>
<th>Side-effect</th>
<th>Frequency (and drug involved)</th>
<th>Experienced by the patient(√ or x)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>Mild leukopaenia</td>
<td>Relatively frequent</td>
<td>□</td>
</tr>
<tr>
<td></td>
<td>Agranulocytosis</td>
<td>Uncommon</td>
<td>□</td>
</tr>
<tr>
<td></td>
<td>Aplastic anaemia</td>
<td>Very rare</td>
<td>□</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>Very rare</td>
<td>□</td>
</tr>
<tr>
<td></td>
<td>Pancytopenia</td>
<td>Very rare</td>
<td>□</td>
</tr>
<tr>
<td>Skin</td>
<td>Skin rash</td>
<td>Very common</td>
<td>□</td>
</tr>
<tr>
<td></td>
<td>Urticaria</td>
<td>Very common</td>
<td>□</td>
</tr>
<tr>
<td></td>
<td>Itching</td>
<td>Very common</td>
<td>□</td>
</tr>
<tr>
<td></td>
<td>Generalised rash</td>
<td>Very rare</td>
<td>□</td>
</tr>
<tr>
<td></td>
<td>Alopecia</td>
<td>Very rare</td>
<td>□</td>
</tr>
<tr>
<td>Hepatic (liver)</td>
<td>Hepatocellular necrosis</td>
<td>Rare (PTU)</td>
<td>□</td>
</tr>
<tr>
<td></td>
<td>Cholestasis</td>
<td>Very rare (MMI)</td>
<td>□</td>
</tr>
<tr>
<td>Collagen</td>
<td>Arthralgia</td>
<td>Common</td>
<td>□</td>
</tr>
<tr>
<td></td>
<td>SLE-like syndrome</td>
<td>Very rare (PTU &gt; MMI)</td>
<td>□</td>
</tr>
<tr>
<td></td>
<td>Vasculitits</td>
<td>Very rare (PTU)</td>
<td>□</td>
</tr>
<tr>
<td>Embryopathy</td>
<td>Choanal atresia, oesophageal atresia, cardiac defects and aplasia cutis</td>
<td>Very rare (MMI)</td>
<td>□</td>
</tr>
<tr>
<td></td>
<td>Situs inversus ± dextrocardia, unilateral kidney agenesis/dysgenesis, and cardiac outflow tract defect</td>
<td>Very rare (PTU, uncertain)</td>
<td>□</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Loss of taste</td>
<td>Rare (MMI)</td>
<td>□</td>
</tr>
<tr>
<td></td>
<td>Hypothrombinaemia</td>
<td>Rare (PTU)</td>
<td>□</td>
</tr>
<tr>
<td></td>
<td>Insulin auto-antibodies</td>
<td>Very rare</td>
<td>□</td>
</tr>
</tbody>
</table>

MMI: methimazole, PTU: propylthiouracil, SLE: systemic lupus erythematosus
function. Administering the incorrect dosage or not monitoring it can produce hypothyroidism, or even goitre. Treatment with ATDs will normally last for 12-18 months.7,10

**Side-effects experienced with antithyroid drugs**

Antithyroid drugs are associated with side-effects which may range from being minor to being potentially life-threatening or even lethal. Methimazole has dose-related side-effects, whereas the side-effects of PTU seem to be less associated with the actual dosage. The milder side-effects are usually self-limiting and observed in less than 5% of cases. They seem to occur during the initial phases of treatment when the daily administered dosage is higher than usual.7,10

When more severe side-effects are experienced with one agent, another thionamide can serve as a substitute. However, cross-sensitivity has been described in as many as 50% of patient cases.5,7,10 Side-effects should be evaluated, and if serious, the drug should be discontinued. Side-effects of the ATDs are listed in Table II and have been provided in the form of a checklist which may be utilised by the pharmacist in the practice setting.7,10

**β-blockers**

β-adrenergic blockers are used in the symptomatic management of hyperthyroidism because of Graves’ disease or toxic nodules requiring surgery. They are used to reduce the sympathomimetic symptoms induced by hyperthyroidism, such as palpitations, anxiety and tremors, and should be discontinued once the patient becomes euthyroid. All β-blockers may be used in the management of hyperthyroidism. Atenolol and nadolol may improve compliance as they only necessitate a once-daily dosing routine. β-blockers should still be used with caution in patients with asthma and heart failure as co-morbid conditions.10

**Radioactive iodine**

Recurrent hyperthyroidism and Graves’ disease may be treated with being克拉素 or being potentially life-threatening or even lethal. Methimazole has dose-related side-effects, whereas the side-effects of PTU seem to be less associated with the actual dosage. The milder side-effects are usually self-limiting and observed in less than 5% of cases. They seem to occur during the initial phases of treatment when the daily administered dosage is higher than usual.7,10

Iodides

Iodine is a temporary solution which inhibits the release of thyroid hormones for only a few days or weeks (1-2 weeks). For this reason, its usefulness is limited to the preparation of patients with Graves’ disease for surgery, as well as the treatment of patients suffering from a thyrotoxic crisis. The inhibitory effect is achieved via the blocking of hormone release, by interfering with hormone biosynthesis through competition with intrathyroidal iodide use. This decreases the size and vascularity of the thyroid gland. Preparations are available as either a saturated potassium iodide solution or as a Lugol’s solution.7,10

**Hypothyroidism**

When hypothyroidism is left untreated, it can result in cardiac failure, psychosis, and coma.11 T4 replacement therapy is highly effective and has been used in its rudimentary form since 1891.11

The major indication for thyroid-replacement therapy remains:12

• Hypothyroidism
• Cretinism
• TSH suppression therapy in patients suffering from thyroid cancer.

Levothyroxine (L.T.) is a synthetic thyroid hormone and remains the drug of choice for thyroid-replacement therapy as it is chemically stable, inexpensive and has uniform potency.13 Dosages of L.T. relate to bodyweight (dosed at 1.8 µg per kg in adults and 0.5 µg per kg in older adults), and is dosed at higher levels in infants and young children.1 When therapy is initiated, it should be at the lower end of the calculated dosage, i.e. the dose should be 125 µg per day for a 70-kg adult.9 It is unnecessary to initiate therapy at 25-50 µg per day and titrate upwards. This also prolongs the desired response to treatment.8,13 Dosages should be titrated using serum thyrotropin concentrations and undertaken 4-6 weeks after a new T4 dosage has been prescribed. Thereafter, this should be carried out annually, or whenever a patient presents with persistent symptoms of either hypo- or hyperthyroidism.12

The target level of treatment is determined by the following:4

• When the patient expresses a sense of well-being, and when signs and symptoms decrease in frequency and severity.
• TSH levels at the lower end of the reference range (0.4-2.5 mU/l). Each patient should be assessed using TSH levels and symptoms,

<table>
<thead>
<tr>
<th>Table III: Patient advice when initiating levothyroxine therapy4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient advice</td>
</tr>
<tr>
<td>It may take a week or more for you to start feeling better. Levothyroxine has a half-life of seven days.</td>
</tr>
<tr>
<td>If you miss one dose, the effect might not be noticeable (because of the long half-life). Take it as soon as you remember to do so.</td>
</tr>
<tr>
<td>Other symptoms, e.g. muscle stiffness, weakness and mental effects, may take several months to resolve once the chemical imbalance has been corrected.</td>
</tr>
<tr>
<td>Levothyroxine should be taken on an empty stomach as this will maximise absorption.</td>
</tr>
<tr>
<td>Treatment will be lifelong and dose adjustments will only be made according to hormone (thyroid) levels. Hormone levels should be assessed once a year.</td>
</tr>
<tr>
<td>The following drugs should be avoided or administered with caution when levothyroxine therapy is being taken:</td>
</tr>
<tr>
<td>• Drugs that will prevent absorption of levothyroxine, e.g. calcium salts, ferrous sulphate, aluminium hydroxide and cholestyramine.</td>
</tr>
<tr>
<td>• Drugs that increase the clearance of levothyroxine, in other words drugs that will cause a decrease in levothyroxine levels, e.g. phenytoin, carbamazepine, phenobarbitone and rifampicin.</td>
</tr>
</tbody>
</table>
and dosed individually. When initiating the therapy, patient counselling should include the advice listed in Table III.

**Side-effects experienced with levothyroxine therapy**

Side-effects experienced with thyroid-replacement therapy relate to excessive thyroid hormone action and may include the following:

- Symptomatic thyrotoxicosis
- Subclinical thyrotoxicosis (with an increase in bone loss)
- Atrial tachyarrhythmias
- Heart failure
- Angina pectoris
- Myocardial infarction.

Patients who were previously diagnosed with underlying ischaemic heart disease may exacerbate myocardial ischemia once euthyroidism has been established. Very rarely, synthetic products produce allergic or idiosyncratic reactions, as were previously experienced with natural or animal-derived products.

Hyperthyroidism may lead to a decrease in bone density because of hyper-remodelling of the cortical and trabecular bone, which can result in an increased likelihood of bone fractures. Acute sympathomimetic symptoms and hair loss have also been experienced after T4 treatment was initiated.

**Conclusion**

The thyroid gland plays a vital role in the maintenance of a normal basal metabolism in the human body. Therefore, abnormalities in thyroid hormone levels can have far-reaching effects on various body systems, organs and tissues. Typically, such abnormalities fall into one of two categories: hypo- or hyperthyroidism, and require effective treatment to either replace the deficient levels of T4 in the bloodstream or to antagonise excessive levels of circulating thyroid hormone. Patients using such therapies over the long term require additional monitoring and support by the multidisciplinary team, including the pharmacist.

**References**