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Hypothyroidism

Hypothyroidism is the clinical syndrome resulting from deficiency of thyroid hormones. It mainly affects women and is more prevalent in the middle-aged and elderly. The symptoms of hypothyroidism may be due to general deceleration of metabolism or to accumulation of mucopolysaccharide in the subcutaneous tissues and vocal cords. Common clinical manifestations include weakness, fatigue, lethargy, physical and mental slowness, and weight gain; puffy, nonpitted swelling of subcutaneous tissue often develops, particularly around the eyes. Menstrual disorders, hyperlipidaemia, and constipation can occur and goitre may develop despite associated cell destruction.

The term **myxoedema** is often reserved for severe or advanced hypothyroidism. In the most severely affected patients, progressive somnolence and torpor combine with cold intolerance and bradycardia to induce a state of coma often known as 'hypothyroid' or 'myxoedema coma' (see below).

In children, untreated hypothyroidism results in retardation of growth and mental development. Endemic cretinism is a result of maternal, and hence fetal, iodine deficiency and consequent lack of thyroid hormone production (see Iodine Deficiency Disorders, p.2170).

Hypothyroidism is usually primary, resulting from malfunction of the thyroid gland. In areas where iodine intake is sufficient the commonest cause of hypothyroidism is auto-immune lymphocytic thyroiditis of which there are two major variants. In **Hashimoto's thyroiditis** there is also goitre whereas in **idiopathic** or **primary myxoedema** (**atrophic thyroiditis**) there is no thyroid enlargement. Hypothyroidism can also be caused by either an excess or a deficiency of iodine. An excess may result from intake of iodine or its salts or iodine-containing drugs such as amiodarone. Drugs that decrease thyroid hormone synthesis such as lithium can also be a cause of hypothyroidism. In some patients hypothyroidism may be secondary to disorders of the hypothalamus or pituitary gland.

The **diagnosis** of hypothyroidism is essentially clinical but, given the non-specific nature of many of the symptoms, biochemical tests are performed for confirmation.[1-3] A raised thyroid stimulating hormone (TSH) value and a low free T_4 or T_3 concentration indicates primary hypothyroidism. Protirelin and thyrotrophin have also been used for the differential diagnosis of hypothyroidism.

Subclinical hypothyroidism is a condition in which there are normal concentrations of thyroid hormones, raised concentrations of TSH, but no clinical symptoms. Patients with subclinical hypothyroidism are at a greater risk of developing clinical hypothyroidism if they also have thyroid antibodies against thyroid peroxidase/microsomal antigen, although the best strategy for identifying those at risk is not yet known.[2]

Hypothyroidism is readily **treated** by lifelong replacement therapy with levothyroxine.[1,2,4-7] Although the thyroid gland produces both T_3 (liothyronine) and T_4 (thyroxine), T_3 is mainly produced by peripheral monodeiodination of circulating T_4 and it is therefore sufficient to give levothyroxine alone. There is no rationale for the use of combined preparations containing liothyronine and levothyroxine, or of dried thyroid hormone extracts, which may lead to elevated serum concentrations of T_3 and thyrotoxic symptoms. Liothyronine may, however, be used initially for its rapid onset of action in severe hypothyroid states such as myxoedema coma (see below). Initial checks should be made to ensure that thyroid replacement treatment is restoring deficiencies in thyroid hormone but not providing an excess. This is best done by monitoring hormone concentrations and the goal of replacement therapy is a normal TSH value, which is generally associated with a normal or slightly elevated T_4 value.[2,5]

In subclinical hypothyroidism, treatment with levothyroxine is controversial. It has been recommended[2-4,7,8] if antibodies to thyroid peroxidase are present, or if TSH levels are above 10 milliunits/litre. Some also recommend treatment if TSH levels are between 5 and 10 milliunits/litre and goitre or antibodies (or both) are evident.[7]

Although titres of antithyroid antibodies may fall during **pregnancy**, some patients may require progressive increases in levothyroxine dosage,[9,10] and therefore it has been recommended that thyroid function tests should be performed in each trimester;[1,2,4,11] some[7,12] currently advocate monitoring every 6 to 8 weeks.

The diagnosis of **congenital hypothyroidism** (neonatal hypothyroidism) is now most commonly made on the basis of screening programmes.[13] Early treatment with adequate doses of levothyroxine is required to minimise the effects of hypothyroidism on mental and physical development. It should be started as soon as possible after birth and should be reviewed regularly.[13,14] However, it is generally accepted that in those with more severe hypothyroidism at diagnosis some small degree of deficit and incoordination remains, although they should be mild enough to permit a normal life.[15]

Hypothyroid (myxoedema) coma is a medical emergency requiring prompt treatment usually with liothyronine given by intravenous injection because of its rapid action, although some centres use intravenous levothyroxine. Alternatively, the nasogastric route may be used. Other treatment includes intravenous hydrocortisone (because of the likelihood of adrenocortical insufficiency) and intravenous fluids (to maintain plasma-glucose and electrolyte concentrations). Respiratory function should be supported by assisted ventilation and oxygen. Hypothyroid coma carries a poor prognosis, with mortality around 50% even with treatment.

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Benzylthiouracil

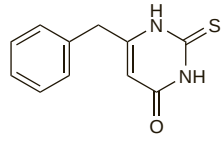
Benciltiouracilo. 6-Benzyl-2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one; 6-Benzyl-2-mercaptopyrimidin-4-ol; 6-Benzyl-2-thiouracil.

$C_{11}H_{10}N_2OS$ = 218.3.

CAS — 33086-27-0; 6336-50-1.

ATC — H03BA03.

ATC Vet — QH03BA03.



Profile

Benzylthiouracil is a thiourea antithyroid drug. It is given by mouth in the treatment of hyperthyroidism (p.2165) in an initial dose of 150 to 200 mg daily, reducing to a maintenance dose of 100 mg daily; it is given in divided doses, preferably with food.

Porphyria. Benzylthiouracil is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Basdene.

Carbimazole *(BAN, rINN)*

Carbimazol; Carbimazolum; Karbimatsoli; Karbimazol; Karbimazolas. Ethyl 3-methyl-2-thioxo-4-imidazoline-1-carboxylate.

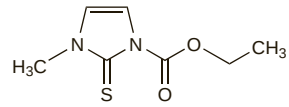
Карбимазол

$C_7H_{10}N_2O_2S$ = 186.2.

CAS — 22232-54-8.

ATC — H03BB01.

ATC Vet — QH03BB01.



Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Carbimazole). A white or yellowish-white crystalline powder. Slightly soluble in water; soluble in alcohol and in acetone.

Adverse Effects and Precautions

Adverse effects from carbimazole and other thiourea antithyroid drugs occur most frequently during the first 8 weeks of treatment. The most common minor adverse effects are nausea and vomiting, gastric discomfort, headache, arthralgia, skin rashes, and pruritus. Hair loss has also been reported.

Bone-marrow depression may occur and mild leucopenia is common. Rarely, agranulocytosis can develop, and is the most serious adverse reaction associated with this class of drugs. Patients or their carers should be told how to recognise such toxicity and should be advised to seek immediate medical attention if mouth ulcers or sore throat, fever, bruising, malaise, or non-specific illness develop. Full blood counts should be performed, and treatment should be stopped immediately if there is any clinical or laboratory evidence of neutropenia. Aplastic anaemia or isolated thrombocytopenia have been reported rarely, as has hypoprothrombinaemia.

There have been several reports of liver damage, most commonly jaundice, in patients taking thiourea antithyroid drugs; the drug should be withdrawn if hepatic effects occur.

Other adverse effects sometimes observed with the thiourea antithyroid compounds include fever, a lupus-like syndrome, myopathy, vasculitis and nephritis, and taste disturbances. Creatine phosphokinase values should be measured if patients experience myalgia.

Excessive doses of antithyroid drugs may cause hypothyroidism and goitre. High doses in pregnancy may result in fetal hypothyroidism and goitre (see Pregnancy, below).

An immune mechanism has been implicated in many of these reactions and cross-sensitivity between the thiourea antithyroid drugs may occur.

Breast feeding. The safety of breast feeding during maternal treatment depends partly on how much drug is distributed into the breast milk. Thiourea antithyroid drugs may be used with care in breast-feeding mothers; neonatal development and thyroid function of the infant should be closely monitored and the lowest effective dose used.

Propylthiouracil has been preferred to carbimazole or thiamazole since it enters breast milk less readily.[1-3] In a small study[4] of breast-feeding mothers taking doses of propylthiouracil as high as 750 mg daily for Graves' disease, no adverse effects were observed on the thyroid status of their infants.

Thiamazole enters breast milk freely, with plasma to milk ratios of almost one.[3,5] The infant's intake of thiamazole after maternal use of carbimazole (or thiamazole) might be greatly reduced by discarding the breast milk produced 2 to 4 hours after a dose,[6] since the highest concentration was found at this time. Two studies found no adverse effects on thyroid function,[7,8] thyroid hormone levels,[7] or physical and intellectual development, in breast-