36. Masiukiewicz US, Burrow GN. Hyperthyroidism in pregnancy: diagnosis and treatment. *Thyroid* 1999; **9:** 647–52.
37. Ogilvy-Stuart AL. Neonatal thyroid disorders. *Arch Dis Child Fetal Neonatal Ed* 2002; **87:** F165–F171.
38. Char DH. Thyroid eye disease. *Br J Ophthalmol* 1996; **80:** 922–6.
39. Fleck BW, Toft AD. Graves' ophthalmopathy. *BMJ* 1990; **300:** 1352–3.
40. Hart RH, Perros P. Glucocorticoids in the medical management of Graves' ophthalmopathy. *Minerva Endocrinol* 2003; **28:** 223–31.

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.

1. Singer PA, *et al.* Treatment guidelines for patients with hyperthyroidism and hypothyroidism. *JAMA* 1995; **273:** 808–12. Also available at: http://www.thyroid.org/professionals/publications/documents/GuidelinesHyperHypo_1995.pdf (accessed 18/05/05)
2. Lindsay RS, Toft AD. Hypothyroidism. *Lancet* 1997; **349:** 413–17. Correction. *ibid.*; 1023.
3. Woeber KA. Update on the management of hyperthyroidism and hypothyroidism. *Arch Intern Med* 2000; **160:** 1067–71.
4. Vanderpump MPJ, *et al.* Consensus statement for good practice and audit measures in the management of hypothyroidism and hyperthyroidism. *BMJ* 1996; **313:** 539–44.
5. Toft AD. Thyroxine therapy. *N Engl J Med* 1994; **331:** 174–80.
6. Roberts CGP, Ladenson PW. Hypothyroidism. *Lancet* 2004; **363:** 793–803.
7. AACE Thyroid Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocr Pract* 2002; **8:** 457–69. Also available at: http://www.aace.com/pub/pdf/guidelines/hypo_hyper.pdf (accessed 07/04/06)
8. Surks MI, *et al.* Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 2004; **291:** 228–38.
9. Drake WM, Wood DF. Thyroid disease in pregnancy. *Postgrad Med J* 1998; **74:** 583–6.
10. Alexander EK, *et al.* Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med* 2004; **351:** 241–9.
11. Girling JC. Thyroid disease in pregnancy. *Hosp Med* 2000; **61:** 834–40.
12. Surks MI, *et al.* Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 2004; **291:** 228–38.
13. LaFranchi S. Congenital hypothyroidism: etiologies, diagnosis, and management. *Thyroid* 1999; **9:** 735–40.
14. Hopwood NJ. Treatment of the infant with congenital hypothyroidism. *J Pediatr* 2002; **141:** 752–4.
15. Rovet JF. Congenital hypothyroidism: long term outcome. *Thyroid* 1999; **9:** 741–8.

Benzylthiouracil

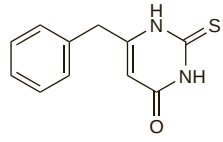
Benciltiouracilo. 6-Benzyl-2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one; 6-Benzyl-2-mercaptopyrimidin-4-ol; 6-Benzyl-2-thiouracil.

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

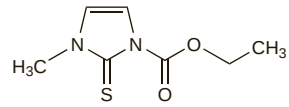
Карбимазол

$C_7H_{10}N_2O_2S$ = 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 nonspecific 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-

fed infants during up to 6 months[7] to 1 year[8] of maternal treatment with thiamazole. Maximum maternal daily doses of 10 mg of thiamazole,[3] 15 mg of carbimazole, and 150 mg of propylthiouracil[9] have been recommended, although thiamazole 20 to 30 mg has been given to thyrotoxic lactating women for the first month of a year of therapy with no observable adverse effects on the thyroid function of their breast-fed infants.[10] Despite stating that goitre has been associated with the use of carbimazole, the American Academy of Pediatrics considers the use of all three drugs to be compatible with breast feeding.[11]

1. Kampmann JP, *et al.* Propylthiouracil in human milk: revision of a dogma. *Lancet* 1980; **i:** 736–8.
2. Johansen K, *et al.* Excretion of methimazole in human milk. *Eur J Clin Pharmacol* 1982; **23:** 339–41.
3. Cooper DS. Antithyroid drugs: to breast-feed or not to breast-feed. *Am J Obstet Gynecol* 1987; **157:** 234–5.
4. Momotani N, *et al.* Thyroid function in wholly breast-feeding infants whose mothers take high doses of propylthiouracil. *Clin Endocrinol (Oxf)* 2000; **53:** 177–81.
5. Cooper DS, *et al.* Methimazole pharmacology in man: studies using a newly developed radioimmunoassay for methimazole. *J Clin Endocrinol Metab* 1984; **58:** 473–9.
6. Rylance GW, *et al.* Carbimazole and breastfeeding. *Lancet* 1987; **i:** 928.
7. Azizi F. Effect of methimazole treatment of maternal thyrotoxicosis on thyroid function in breast-feeding infants. *J Pediatr* 1996; **128:** 855–8.
8. Azizi F, *et al.* Thyroid function and intellectual development of infants nursed by mothers taking methimazole. *J Clin Endocrinol Metab* 2000; **85:** 3233–8.
9. Lamberg B-A, *et al.* Antithyroid treatment of maternal hyperthyroidism during lactation. *Clin Endocrinol (Oxf)* 1984; **21:** 81–7.
10. Azizi F, Hedayati M. Thyroid function in breast-fed infants whose mothers take high doses of methimazole. *J Endocrinol Invest* 2002; **25:** 493–6.
11. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 18/05/05)

Effects on the blood. While **leucopenia** is considered to be a common adverse effect of the thiourea antithyroid drugs, occurring in up to a quarter of patients, it is usually mild and improves as treatment continues.[1]

Agranulocytosis, a more serious hazard, is usually reported to affect 0.03% of patients in Europe,[2] who are mostly treated with carbimazole. However, the incidence has been reported to be higher (0.4%) in areas where thiamazole is used.[3,4] Fatalities have been reported.[1,2,4,5] Although a direct toxic effect had been suggested, the agranulocytosis associated with the thiourea drugs is generally considered to be immunologically mediated.[1,6] The onset of agranulocytosis is usually rapid and monitoring of the blood count is not always of predictive value;[3] routine monitoring is not indicated.[2] Agranulocytosis has occurred in patients receiving propylthiouracil for a second time who had no such complications in their first course of therapy.[7] There is limited evidence that agranulocytosis is more common at higher doses, and in older patients. However, this has not been proved conclusively.[1]

There have been some case reports of **aplastic anaemia** being produced by antithyroid drugs, but the excess risk associated with their use is considered to be very low[6,8] and complete recovery has been reported after withdrawal of the antithyroid drug. An immune mechanism has been implicated.

Carbimazole has produced **haemolytic anaemia**.[9] In this case the immune reaction was specific to carbimazole and could not be demonstrated with thiamazole.

On very rare occasions patients taking propylthiouracil have experienced a reduction in prothrombin values and bleeding.[10-12] In one patient bleeding was linked to propylthiouracil-induced **thrombocytopenia**.[13]

1. Bartalena L *et al.* Adverse effects of thyroid hormone preparations and antithyroid drugs. *Drug Safety* 1996; **15:** 53–63.
2. Committee on Safety of Medicines/Medicines Control Agency. Reminder: agranulocytosis with antithyroid drugs. *Current Problems* 1999; **25:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023233&RevisionSelectionMethod=LatestReleased (accessed 17/05/06)
3. Tajiri J, *et al.* Antithyroid drug-induced agranulocytosis: the usefulness of routine white blood cell count monitoring. *Arch Intern Med* 1990; **150:** 621–4.
4. Anonymous. Elaboration: drug-induced agranulocytosis–monitoring antithyroid treatment. *Drug Ther Bull* 1997; **35:** 88.
5. Anonymous. Drug-induced agranulocytosis. *Drug Ther Bull* 1997; **35:** 49–52.
6. International Agranulocytosis and Aplastic Anaemia Study. Risk of agranulocytosis and aplastic anaemia in relation to use of antithyroid drugs. *BMJ* 1988; **297:** 262–5.
7. Shiran A, *et al.* Propylthiouracil-induced agranulocytosis in four patients previously treated with the drug. *JAMA* 1991; **266:** 3129–30.
8. Bishara J. Methimazole-induced aplastic anemia. *Ann Pharmacother* 1996; **30:** 684.
9. Salama A, *et al.* Carbimazole-induced immune haemolytic anaemia: role of drug-red blood cell complexes for immunization. *Br J Haematol* 1988; **68:** 479–82.
10. D'Angelo G, Le Gresley LP. Severe hypoprothrombinaemia after propylthiouracil therapy. *Can Med Assoc J* 1959; **81:** 479–81.
11. Naeye RL, Terrien CM. Hemorrhagic state after therapy with propylthiouracil. *Am J Clin Pathol* 1960; **34:** 254–7.
12. Gotta AW, *et al.* Prolonged intraoperative bleeding caused by propylthiouracil-induced hypoprothrombinemia. *Anesthesiology* 1972; **37:** 562–3.
13. Ikeda S, Schweiss JF. Excessive blood loss during operation in the patient treated with propylthiouracil. *Can Anaesth Soc J* 1982; **29:** 477–80.

Effects on the ears. Earache, high-frequency hearing loss, and tinnitus in a patient with Graves' disease were attributed to hypersensitivity to carbimazole;[1] hearing loss, but not the tinnitus, resolved when carbimazole was replaced with propylthiouracil.

1. Hill D, *et al.* Hearing loss and tinnitus with carbimazole *BMJ* 1994; **309:** 929.

Effects on the kidneys. Glomerulonephritis associated with the development of antineutrophil cytoplasmic antibodies has been reported in patients receiving thiourea antithyroid drugs.[1-5]

1. Vogt BA, *et al.* Antineutrophil cytoplasmic autoantibody-positive crescentic glomerulonephritis as a complication of treatment with propylthiouracil in children. *J Pediatr* 1994; **124:** 986–8.
2. D'Cruz D, *et al.* Antineutrophil cytoplasmic antibody-positive crescentic glomerulonephritis associated with anti-thyroid drug treatment. *Br J Rheumatol* 1995; **34:** 1090–1.
3. Yuasa S, *et al.* Antineutrophil cytoplasmic antibodies (ANCA)-associated crescentic glomerulonephritis and propylthiouracil therapy. *Nephron* 1996; **73:** 701–3.
4. Kudoh Y, *et al.* Propylthiouracil-induced rapidly progressive glomerulonephritis associated with antineutrophil cytoplasmic autoantibodies. *Clin Nephrol* 1997; **48:** 41–3.
5. Prasad GVR, *et al.* Propylthiouracil-induced diffuse proliferative lupus nephritis: review of immunological complications. *J Am Soc Nephrol* 1997; **8:** 1205–10.

Effects on the liver. Jaundice, usually cholestatic, has been reported with thiamazole and carbimazole.[1-5] An immune-mediated mechanism rather than a toxic reaction has been proposed. Hepatitis (sometimes progressing to cirrhosis[6]) and hepatic necrosis have been associated with propylthiouracil,[6-9] sometimes with fatal consequences.[7,8] However, in one study[10] almost 30% of patients being treated with propylthiouracil developed asymptomatic liver changes (increased alanine aminotransferase values). Dose reduction resulted in a return to normal values in 13 of the 15 patients affected.

Despite reports of liver damage, propylthiouracil has been investigated in the treatment of patients with alcoholic liver disease (see p.2175).

1. Becker CE, *et al.* Hepatitis from methimazole during adrenal steroid therapy for malignant exophthalmos. *JAMA* 1968; **206:** 1787–9.
2. Fischer MG, *et al.* Methimazole-induced jaundice. *JAMA* 1973; **223:** 1028–9.
3. Blom H, *et al.* A case of carbimazole-induced intrahepatic cholestasis. *Arch Intern Med* 1985; **145:** 1513–15.
4. Schmidt G, *et al.* Methimazole-associated cholestatic liver injury: case report and brief literature review. *Hepatogastroenterology* 1986; **33:** 244–6.
5. Arab DM, *et al.* Severe cholestatic jaundice in uncomplicated hyperthyroidism treated with methimazole. *J Clin Endocrinol Metab* 1995; **80:** 1083–5.
6. Özenírler S, *et al.* Propylthiouracil-induced hepatic damage. *Ann Pharmacother* 1996; **30:** 960–3.
7. Hanson JS. Propylthiouracil and hepatitis. Two cases and a review of the literature. *Arch Intern Med* 1984; **144:** 994–6.
8. Limaye A, Ruffolo PR. Propylthiouracil-induced fatal hepatic necrosis. *Am J Gastroenterol* 1987; **82:** 152–4.
9. Ichiki Y, *et al.* Propylthiouracil-induced severe hepatitis: a case report and review of the literature. *J Gastroenterol* 1998; **33:** 747–50.
10. Liaw Y-F, *et al.* Hepatic injury during propylthiouracil therapy in patients with hyperthyroidism. *Ann Intern Med* 1993; **118:** 424–8.

Effects on the lungs. Diffuse interstitial pneumonitis occurred in 2 patients given propylthiouracil[1] and a hypersensitivity reaction was suggested. Propylthiouracil was also implicated in 2 cases of alveolar haemorrhage associated with antineutrophil cytoplasmic antibody.[2,3]

1. Miyazono K, *et al.* Propylthiouracil-induced diffuse interstitial pneumonitis. *Arch Intern Med* 1984; **144:** 1764–5.
2. Ohtsuka M, *et al.* Propylthiouracil-induced alveolar haemorrhage associated with antineutrophil cytoplasmic antibody. *Eur Respir J* 1997; **10:** 1405–7.
3. Dhillon SS, *et al.* Diffuse alveolar hemorrhage and pulmonary capillaritis due to propylthiouracil. *Chest* 1999; **116:** 1485–8.

Effects on the muscles. Myositis with pain, weakness, and increased creatine kinase concentrations has been reported with carbimazole.[1,2] This effect might be explained by 'tissue hypothyroidism', and might respond to dosage reduction.[3]

1. Page SR, Nussey SS. Myositis in association with carbimazole therapy. *Lancet* 1989; **i:** 964.
2. Pasquier E, *et al.* Biopsy-proven myositis with microvasculitis in association with carbimazole. *Lancet* 1991; **338:** 1082–3.
3. O'Malley B. Carbimazole-induced cramps. *Lancet* 1989; **i:** 1456.

Hypersensitivity. Many of the adverse effects associated with the thiourea antithyroid drugs appear to have an immune basis. These effects may be associated with polyarthritis[1] or hypersensitivity vasculitis.[2-7] The latter is sometimes severe and multisystemic, and fatalities have occurred.

Hypersensitivity reactions may also be associated with the development of antineutrophil cytoplasmic antibodies (ANCA), or sometimes with a lupus-like syndrome with or without the presence of antinuclear antibodies.[2,5]

Serum sickness with arthralgias and raised immunoglobulin M (IgM) concentrations has been reported with thiamazole,[8] and the production of antibodies to insulin, resulting in episodes of hypoglycaemia, has been associated with thiamazole[9] and carbimazole.[10]

The thiourea antithyroid drugs all contain a thioamide group and cross-sensitivity between them might be expected. In particular, complete cross-reactivity may be expected between thiamazole and carbimazole since the latter is converted *in vivo* to thiamazole, although one report[11] suggests this is not necessarily the case. Cross-sensitivity between propylthiouracil and carbimazole[12] or thiamazole[13] has been reported but the incidence and clinical importance is not clear. Although it has been suggested that carbimazole or thiamazole may be substituted for propylthiouracil in hypersensitive patients, it is safer to stop antithyroid drugs in such patients.[12]

1. Bajaj S, *et al.* Antithyroid arthritis syndrome. *J Rheumatol* 1998; **25:** 1235–9.
2. Kawachi Y, *et al.* ANCA-associated vasculitis and lupus-like syndrome caused by methimazole. *Clin Exp Dermatol* 1995; **20:** 345–7.
3. Chastain MA, *et al.* Propylthiouracil hypersensitivity: report of two patients with vasculitis and review of the literature. *J Am Acad Dermatol* 1999; **41:** 757–64.
4. Gunton JE, *et al.* Clinical case seminar: antithyroid drugs and antineutrophil cytoplasmic antibody positive vasculitis. A case report and review of the literature. *J Clin Endocrinol Metab* 1999; **84:** 13–16.
5. Mathieu E, *et al.* Systemic adverse effect of antithyroid drugs. *Clin Rheumatol* 1999; **18:** 66–8.
6. Dolman KM, *et al.* Vasculitis and antineutrophil cytoplasmic autoantibodies associated with propylthiouracil therapy. *Lancet* 1993; **342:** 651–2.
7. ten Holder SM, *et al.* Cutaneous and systemic manifestations of drug-induced vasculitis. *Ann Pharmacother* 2002; **36:** 130–47.
8. Van Kuyk M, *et al.* Methimazole-induced serum sickness. *Acta Clin Belg* 1983; **38:** 68–9.
9. Hakamata M, *et al.* Insulin autoimmune syndrome after the third therapy with methimazole. *Intern Med* 1995; **34:** 410–12.
10. Burden AC, Rosenthal FD. Methimazole and insulin autoimmune syndrome. *Lancet* 1983; **ii:** 1311.
11. Kroll H, *et al.* Drug-dependent antibodies against the prodrug carbimazole do not react with the metabolite thiamazole. *Blood* 2001; **97:** 2186–7.
12. Smith A, *et al.* Cross sensitivity to antithyroid drugs. *BMJ* 1989; **298:** 1253.
13. De Weweire A, *et al.* Failure to control hyperthyroidism with a thionamide after potassium perchlorate withdrawal in a patient with amiodarone associated thyrotoxicosis. *J Endocrinol Invest* 1987; **10:** 529.

Pregnancy. Thiourea antithyroid drugs have been used successfully in pregnancy (see Hyperthyroidism, p.2165).

Thiamazole (the metabolite of carbimazole) has been the drug most frequently involved in the few reports of **congenital defects** following maternal use of such compounds. Several infants exposed to thiamazole *in utero* have been born with scalp defects (aplasia cutis congenita—a localised absence of skin at birth)[1,2] although hyperthyroidism itself may give rise to such defects.[3] Individual cases of other congenital defects associated with thiamazole have included choanal atresia (an upper respiratory-tract defect), oesophageal atresia, and tracheo-oesophageal fistula[3] but the incidence of congenital abnormalities is not increased compared with the general population.[4] Gastroschisis (an abdominal wall defect) has been reported in an infant after maternal exposure to carbimazole.[5] There have been some reports of neonates exposed to thiourea antithyroid drugs *in utero* displaying signs of **hypothyroidism** including goitre.[6,7]

1. Milham S. Scalp defects in infants of mothers treated for hyperthyroidism with methimazole or carbimazole during pregnancy. *Teratology* 1985; **32:** 321.
2. Vogt T, *et al.* Aplasia cutis congenita after exposure to methimazole: a causal relationship? *Br J Dermatol* 1995; **133:** 994–6.
3. Johnsson E, *et al.* Severe malformations in infant born to hyperthyroid woman on methimazole. *Lancet* 1997; **350:** 1520.
4. Wing DA, *et al.* A comparison of propylthiouracil versus methimazole in the treatment of hyperthyroidism in pregnancy. *Am J Obstet Gynecol* 1994; **170:** 90–5.
5. Guignon A-M, *et al.* Carbimazole-related gastroschisis. *Ann Pharmacother* 2003; **37:** 829–31.
6. O'Doherty MJ, *et al.* Treating thyrotoxicosis in pregnant or potentially pregnant women. *BMJ* 1999; **318:** 5–6.
7. Masiukiewicz US, Barrow GN. Hyperthyroidism in pregnancy: diagnosis and treatment. *Thyroid* 1999; **9:** 647–52.

Pharmacokinetics

The pharmacokinetics of carbimazole and thiamazole can be considered together since carbimazole is rapidly and completely metabolised to thiamazole in the body. The antithyroid activity of carbimazole is dependent upon this conversion to thiamazole.

Carbimazole and other thiourea antithyroid drugs are rapidly absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 1 to 2 hours after oral doses.

They are concentrated in the thyroid gland; since their duration of action is more closely related to the intrathyroidal drug concentration than their plasma half-life, prolonged antithyroid activity results from single daily doses. Thiamazole is not bound to plasma proteins.

Thiamazole has an elimination half-life from plasma of about 3 to 6 hours and is metabolised, probably by the

liver, and excreted in the urine. Less than 12% of a dose of thiamazole may be excreted as unchanged drug. 3-Methyl-2-thiohydantoin has been identified as a metabolite of thiamazole. The elimination half-life may be increased in hepatic and renal impairment.

Thiamazole crosses the placenta and is distributed into breast milk.

◊ References to the pharmacokinetics of carbimazole and thiamazole.

1. Skellern GG, *et al.* The pharmacokinetics of methimazole after oral administration of carbimazole and methimazole, in hyperthyroid patients. *Br J Clin Pharmacol* 1980; **9:** 137–43.
2. Kampmann JP, Hansen JM. Clinical pharmacokinetics of antithyroid drugs. *Clin Pharmacokinet* 1981; **6:** 401–28.
3. Jansson R, *et al.* Intrathyroidal concentrations of methimazole in patients with Graves' disease. *J Clin Endocrinol Metab* 1983; **57:** 129–32.
4. Cooper DS, *et al.* Methimazole pharmacology in man: studies using a newly developed radioimmunoassay for methimazole. *J Clin Endocrinol Metab* 1984; **58:** 473–9.
5. Jansson R, *et al.* Pharmacokinetic properties and bioavailability of methimazole. *Clin Pharmacokinet* 1985; **10:** 443–50.

Uses and Administration

Carbimazole is a thiourea antithyroid drug that acts by blocking the production of thyroid hormones (see p.2165). It is used in the management of hyperthyroidism (p.2165), including the treatment of Graves' disease, the preparation of hyperthyroid patients for thyroidectomy, as an adjunct to radio-iodine therapy, and in the treatment of thyroid storm.

Carbimazole is completely metabolised to thiamazole and it is this metabolite that is responsible for the antithyroid activity of carbimazole.

Carbimazole is given orally in a typical initial dosage of 15 to 40 mg daily, in divided doses; occasionally up to 60 mg daily may be required. Control of symptoms is usually achieved in 1 to 2 months. When the patient is euthyroid the dose is gradually reduced to the smallest amount that will maintain the euthyroid state. Typical maintenance doses are 5 to 15 mg daily, which may be given as a single daily dose.

Treatment in children should be undertaken by a specialist. The *BNFC* recommends an initial dose of 250 micrograms/kg three times daily for neonates and children up to 12 years of age. Children aged 12 to 18 years may be given 10 mg three times daily initially. Doses are adjusted according to response; higher initial doses may be needed in thyrotoxic crisis.

Carbimazole is also given orally in a dose of 20 to 60 mg daily, with supplemental levothyroxine, as a *blocking-replacement regimen*.

Either form of maintenance treatment is usually continued for at least a year, and often for 18 months; up to 2 years of treatment may be required.

Preparations

BP 2008: Carbimazole Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Neo-Mercazole; ***Austria:*** Carbistad; ***Denm.:*** Neo-Mercazole; ***Fin.:*** Tyrazol; ***Fr.:*** Neo-Mercazole; ***Ger.:*** Car; Neo-Thyreostat†; ***Gr.:*** Thyrostat; ***Hong Kong:*** Cazole; ***India:*** Neo-Mercazole; ***Indon.:*** Neo-Mercazole; ***Irl.:*** Neo-Mercazole; ***Malaysia:*** Camazol†; ***Norw.:*** Neo-Mercazole; ***NZ:*** Neo-Mercazole; ***Philipp.:*** Neo-Mercazole; ***S.Afr.:*** Neo-Mercazole; ***Singapore:*** Camazol; Cazole†; ***Spain:*** Neo Tomizol; ***Switz.:*** Neo-Mercazole; ***UK:*** Neo-Mercazole.

Dibromotyrosine

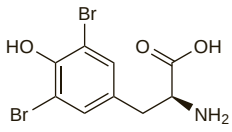
Dibromotirosina. 3,5-Dibromo-L-tyrosine.

$C_9H_9Br_2NO_3$ = 339.0.

CAS — 300-38-9.

ATC — H03BX02.

ATC Vet — QH03BX02.



Profile

Dibromotyrosine is an antithyroid drug used in the treatment of hyperthyroidism (p.2165) in doses of 300 to 900 mg daily by mouth.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Bromotiren.

Multi-ingredient: ***Ital.:*** Bromazolo.

Iodine

Iod; Iode; Iodium; Iodo; Iodum; Iyot; Jód; Jod; Jodas; Jodi; Jodum; Yodo.

I_2 = 253.80894.

CAS — 7553-56-2.

ATC — D08AG03.

ATC Vet — QD08AG03.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Iodine). Greyish-violet, brittle plates or fine crystals, with a metallic sheen. It is slowly volatile at room temperature. Very slightly soluble in water; soluble in alcohol; slightly soluble in glycerol; very soluble in concentrated solutions of iodides.

USP 31 (Iodine). Heavy, greyish-black plates or granules with a metallic sheen and a characteristic odour. Soluble 1 in 3000 of water, 1 in 13 of alcohol, 1 in 4 of carbon disulfide, and 1 in 80 of glycerol; freely soluble in chloroform, in ether, and in carbon tetrachloride; soluble in solutions of iodides. Store in airtight containers.

Incompatibility. With acetone, iodine forms a pungent irritating compound.

Potassium Iodate

Iodato potásico; Potasu jodan.

KIO_3 = 214.0.

CAS — 7758-05-6.

Pharmacopoeias. In *Br.*, *Chin.*, and *It.*

BP 2008 (Potassium Iodate). A white crystalline powder with a slight odour. Slowly soluble in water; insoluble in alcohol. A 5% solution in water has a pH of 5.0 to 8.0.

Potassium Iodide

Iodeto de Potássio; Ioduro potásico; Jodid draselný; Kalii Iodetum; Kalii iodidum; Kalii Jodidum; Kalio jodidas; Kalium Iodatum; Kalium Jodatum; Kaliumjodid; Kálium-jodid; Kaliumjodidi; Pot. Iod.; Potassii Iodidum; Potassium (Iodure de); Potassium, iodure de; Potasu jodek; Potasyum Iyodür.

KI = 166.0.

CAS — 7681-11-0.

ATC — R05CA02; S01XA04; V03AB21.

ATC Vet — QR05CA02; QS01XA04; QV03AB21.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Potassium Iodide). A white or almost white powder or colourless crystals. Very soluble in water; soluble in alcohol; freely soluble in glycerol. Protect from light.

USP 31 (Potassium Iodide). Hexahedral crystals, either transparent and colourless or somewhat opaque and white, or a white, granular powder. It is slightly hygroscopic. Soluble 1 in 0.7 of water and 1 in 0.5 of boiling water, 1 in 22 of alcohol, and 1 in 2 of glycerol. Its solutions are neutral or alkaline to litmus.

Sodium Iodide

Iodeto de Sódio; Ioduro sódico; Jodid sodný; Natrii Iodetum; Natrii iodidum; Natrii Jodidum; Natrio jodidas; Natrium Iodatum; Natriumjodid; Nátrium-jodid; Natriumjodidi; Sod. Iod.; Sodii Iodidum; Sodium (Iodure de); Sodium, iodure de; Sodu jodek; Sodyum Iyodür.

NaI = 149.9.

CAS — 7681-82-5.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Sodium Iodide). Colourless crystals or white or almost white, crystalline powder. It is hygroscopic. Very soluble in water; freely soluble in alcohol. Protect from light.

USP 31 (Sodium Iodide). Colourless, odourless crystals, or white crystalline powder. It is deliquescent in moist air and develops a brown tint upon decomposition. Soluble 1 in 0.6 of water, 1 in 2 of alcohol, and 1 in 1 of glycerol. Store in airtight containers.

Adverse Effects and Treatment

Iodine and iodides, whether applied topically or given systemically, can give rise to hypersensitivity reactions which may include urticaria, angioedema, cutaneous haemorrhage or purpuras, fever, arthralgia, lymphadenopathy, and eosinophilia.

Inhalation of iodine vapour is very irritating to mucous membranes.

Iodine and iodides have variable effects on the thyroid (see below) and can produce goitre and hypothyroidism as well as hyperthyroidism (the Iod-Basedow or Jod-Basedow phenomenon). Goitre and hypothyroidism have also occurred in infants born to mothers who had taken iodides during pregnancy.

Prolonged use may lead to a range of adverse effects, often called 'iodism', some of which may again be due to hypersensitivity. Adverse effects include metallic taste, increased salivation, burning or painful mouth; there may be acute rhinitis, coryza-like symptoms, and swelling and inflammation of the throat. Eyes may be irritated and swollen and there may be increased lachrymation. Pulmonary oedema, dyspnoea, and bronchitis may develop. Skin reactions include acneform or, more rarely, severe eruptions (iododerma). Other reported effects include depression, insomnia, impotence, headache, and gastrointestinal disturbances, notably nausea, vomiting, and diarrhoea.

The symptoms of acute poisoning from ingestion of iodine are mainly due to its corrosive effects on the gastrointestinal tract; a disagreeable metallic taste, vomiting, abdominal pain, and bloody diarrhoea occur. Thirst and headache have been reported. Systemic toxicity may lead to shock, tachycardia, hypotension, fever, metabolic acidosis and renal impairment. Death may be due to circulatory failure, oedema of the epiglottis resulting in asphyxia, aspiration pneumonia, or pulmonary oedema. Oesophageal stricture may occur if the patient survives the acute stage.

Victims of acute poisoning have been given copious draughts of milk or starch mucilage; lavage should probably not be attempted, and certainly not unless the ingested iodine was in sufficiently dilute form not to produce gastrointestinal corrosion. Other possible oral treatments include activated charcoal or sodium thiosulfate solution (usually as a 1% solution) to reduce iodine to the less toxic iodides.

Effects on the thyroid. Iodide may be isolated by the body from a variety of sources, including an iodine-rich diet, or some disinfectants and drugs containing iodine (see also under Amiodarone, p.1212). Although iodine is required for the production of thyroid hormones, excessive quantities can cause hyperthyroidism, or even paradoxical goitre and hypothyroidism.

The normal daily requirement ranges from 100 to 300 micrograms.[1,2] Quantities of 500 micrograms to 1 mg daily probably have no untoward effects on thyroid function in most cases.[2] When progressively larger doses are given there is an initial rise in thyroid hormone production, but at still higher doses, production decreases (the Wolff-Chaikoff effect). This effect is usually seen with doses of more than about 2 mg daily, but is normally transient, adaptation occurring on repeated dosage. In certain individuals a lack of adaptation produces a chronic inhibition of thyroid hormone synthesis leading to goitre and **hypothyroidism**.[1,2]

Excess iodine may also induce **hyperthyroidism** (the Iod-Basedow or Jod-Basedow phenomenon). Iodine-induced hyperthyroidism has been associated with iodine prophylaxis programmes in developing countries.[3] The highest incidence of hyperthyroidism has been reported to occur 1 to 3 years after supplementation begins, with the incidence returning to normal within 3 to 10 years despite continued iodine exposure.[4] Elderly subjects and those with nodular goitres have been found to be at greatest risk.

To overcome any adverse effects on thyroid function as a result of iodine prophylaxis during **pregnancy**, WHO has issued guidelines on the safe use of iodised oil during gestation.[5,6] There is some evidence that the use of iodine-containing antiseptics on pregnant women and neonates may cause disturbances in thyroid function.[7,8]

1. Arthur JR, Beckett GJ. Thyroid function. *Br Med Bull* 1999; **55:** 658–68.
2. WHO. Iodine. In *Trace elements in human nutrition and health*. Geneva: WHO, 1996: 49–71.
3. Delange F, *et al.* Risks of iodine-induced hyperthyroidism after correction of iodine deficiency by iodized salt. *Thyroid* 1999; **9:** 545–56.
4. Fradkin JE, Wolff J. Iodide-induced thyrotoxicosis. *Medicine (Baltimore)* 1983; **62:** 1–20.
5. WHO. Safe use of iodized oil to prevent iodine deficiency in pregnant women. *Bull WHO* 1996; **74:** 1–3.
6. Delange F. Administration of iodized oil during pregnancy: a summary of the published evidence. *Bull WHO* 1996; **74:** 101–8.
7. Linder N *et al.* Topical iodine-containing antiseptics and subclinical hypothyroidism in preterm infants. *J Pediatr* 1997; **131:** 434–9.
8. Weber G *et al.* Neonatal transient hypothyroidism: aetiological study. *Arch Dis Child Fetal Neonatal Ed* 1998; **79:** F70–2.