associated with serious dose-related adverse effects. Aplastic anaemia (with some fatalities), agranulocytosis, leucopenia, pancytopenia, and the nephrotic syndrome have been reported. Excessive doses may cause hypothyroidism and goitre.

Effects on the blood. There have been reports of fatal aplastic anaemia[1,2] and of leucopenia and agranulocytosis[1] associated with the use of potassium perchlorate for the treatment of hyperthyroidism. A review[3] in 1998 noted that despite an increase in perchlorate use in recent years there did not appear to have been any further cases of aplastic anaemia since the 1960s.

1. Anonymous. Potassium perchlorate and aplastic anaemia. *BMJ* 1961; **i:** 1520–1.
2. Krevans JR, *et al*. Fatal aplastic anemia following use of potassium perchlorate in thyrotoxicosis. *JAMA* 1962; **181:** 182–4.
3. Wolff J. Perchlorate and the thyroid gland. *Pharmacol Rev* 1998; **50:** 89–105.

Uses and Administration

Potassium and sodium perchlorate reduce the uptake and concentration of iodide, pertechnetate, and other anions by the thyroid, choroid plexus, gastric mucosa, and salivary glands, probably by competitive inhibition of active transport mechanisms.

They are used **diagnostically** as adjuncts to pertechnetate (^{99m}Tc) to enhance visualisation of the brain, Meckel's diverticulum, or the placenta by reducing unwanted images of other organs. The usual oral dose of either potassium or sodium perchlorate is 200 to 400 mg given 30 to 60 minutes before the use of sodium pertechnetate (^{99m}Tc).

Potassium and sodium perchlorate are also used with sodium iodide (^{131}I) in the perchlorate discharge test of thyroid function. The release of radio-iodine from the gland following an oral dose of perchlorate indicates a defect in the binding of iodide by the thyroid and thus a defect in thyroid hormone synthesis. The test has also been used to investigate the action of antithyroid drugs.

Potassium and sodium perchlorate have been used in the treatment of **hyperthyroidism** (p.2165), but because of toxicity have been largely replaced by alternative treatments. However, perchlorates may be useful in patients with iodine-induced hyperthyroidism such as that associated with amiodarone therapy, by increasing responsiveness to conventional antithyroid drugs. A typical dose of potassium perchlorate in amiodarone-induced hyperthyroidism is 1 g daily.

◊ References.

1. Bartalena L, *et al*. Treatment of amiodarone-induced thyrotoxicosis, a difficult challenge: results of a prospective study. *J Clin Endocrinol Metab* 1996; **81:** 2930–3.
2. Wolff J. Perchlorate and the thyroid gland. *Pharmacol Rev* 1998; **50:** 89–105.
3. Soldin OP, *et al*. Perchlorate clinical pharmacology and human health: a review. *Ther Drug Monit* 2001; **23:** 316–31.
4. Bartalena L, *et al*. Diagnosis and management of amiodarone-induced thyrotoxicosis in Europe: results of an international survey among members of the European Thyroid Association. *Clin Endocrinol (Oxf)* 2004; **61:** 494–502.

Preparations

USP 31: Potassium Perchlorate Capsules.

Proprietary Preparations (details are given in Part 3)
Austria: Irenat; ***Cz.:*** Irenat; ***Ger.:*** Irenat; ***Ital.:*** Pertiroid; ***Pol.:*** Irenat; ***USA:*** Perchloracap†.

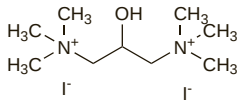
Prolonium Iodide *(rINN)*

Ioduro de prolonio; Prolonii Iodidum; Prolonium, Iodure de. *NN*-(2-Hydroxytrimethylene)bis(trimethylammonium) di-iodide.

Пролония Йодид

$C_9H_{24}I_2N_2O$ = 430.1.

CAS — 123-47-7.



Pharmacopoeias. In *Chin.*

Profile

Prolonium iodide has been given by injection as a source of iodine (p.2169) as part of the treatment of thyroid storm and for the pre-operative management of hyperthyroidism.

Propylthiouracil *(BAN, rINN)*

Proiltiourasil; Propiltiouracil; Propiltiouracilas; Propiltiouracilo; Propylthiouracile; Propylthiouracilum; Propyltiouracil; Propyylitiourasiili. 2,3-Dihydro-6-propyl-2-thioxopyrimidin-4(1*H*)-one; 2-Mercapto-6-propylpyrimidin-4-ol; 6-Propyl-2-thiouracil.

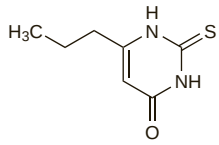
Пропилтиоурацил

$C_7H_{10}N_2OS$ = 170.2.

CAS — 51-52-5.

ATC — H03BA02.

ATC Vet — QH03BA02.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.
Ph. Eur. 6.2 (Propylthiouracil). White or almost white crystals or crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; dissolves in solutions of alkali hydroxides. Protect from light.
USP 31 (Propylthiouracil). A white, powdery, crystalline substance. It is starch-like in appearance and to the touch. Slightly soluble in water, in chloroform, and in ether; sparingly soluble in alcohol; soluble in ammonium hydroxide and in alkali hydroxides. Protect from light.

Adverse Effects and Precautions

As for Carbimazole, p.2167, although cross-sensitivity to carbimazole does not necessarily occur.

Propylthiouracil has been associated with greater hepatotoxicity than other thiourea antithyroid drugs (such as carbimazole or thiamazole). Rarely hepatitis, hepatic necrosis, encephalopathy, and death have occurred; asymptomatic liver damage is more common (see Effects on the Liver, under Carbimazole, p.2168).

Propylthiouracil should be given with care, and in reduced doses, to patients with renal impairment.

Breast feeding. Propylthiouracil has been preferred to carbimazole or thiamazole since it enters breast milk less readily, see Breast Feeding, under Carbimazole, p.2167.

Pharmacokinetics

Propylthiouracil is rapidly absorbed from the gastrointestinal tract with a 50 to 75% bioavailability and with peak plasma concentrations occurring about 2 hours after oral doses. It is concentrated in the thyroid gland; since its duration of action is more closely related to the intrathyroidal drug concentration than its plasma half-life, prolonged antithyroid activity results from single daily doses. Propylthiouracil is about 80% bound to plasma proteins.

Propylthiouracil has an elimination half-life of about 1 to 2 hours. It undergoes rapid first-pass metabolism in the liver, and is mainly excreted in the urine as the glucuronic acid conjugate, with less than 2% excreted as unchanged drug. The elimination half-life may be increased in renal or hepatic impairment.

Propylthiouracil crosses the placenta and is distributed into breast milk.

Uses and Administration

Propylthiouracil is a thiourea antithyroid drug that acts by blocking the production of thyroid hormones (see p.2165); it also inhibits the peripheral deiodination of thyroxine to tri-iodothyronine. It is used in the management of hyperthyroidism (p.2165), including the treatment of Graves' disease, preparation of hyperthyroid patients for thyroidectomy, use as an adjunct to radioiodine therapy, and the treatment of thyroid storm.

Propylthiouracil is usually given orally. Initial doses range from 150 to 450 mg daily (the *BNF* recommends 200 to 400 mg daily), although in severe cases initial doses of 600 to 1200 mg daily have been used. It has often been given in divided daily doses but once daily dosage is also possible. Improvement is usually seen in 1 to 3 weeks and control of symptoms is achieved in 1 to 2 months. When the patient is euthyroid the dose is gradually reduced to a maintenance dose, usually 50 to 150 mg daily. Treatment is usually continued for 1 to 2 years. In the UK, the *BNFC* recommends the following initial doses by mouth for children:

- in neonates: 2.5 to 5 mg/kg twice daily
- in those aged 1 month to 1 year: 2.5 mg/kg three times daily
- in those aged 1 to 5 years: 25 mg three times daily
- in those aged 5 to 12 years: 50 mg three times daily
- in those aged 12 to 18 years: 100 mg three times daily

These doses are given until the patient is euthyroid and then adjusted as needed; higher doses may be required, especially in thyrotoxic crises.

Doses should be reduced in renal impairment (below). Doses may also need to be reduced in hepatic impairment.

Administration in renal impairment. The dosage of propylthiouracil should be reduced in patients with renal impairment according to creatinine clearance (CC) as follows:

- CC 10 to 50 mL/minute, doses should be reduced by 25%
- CC less than 10 mL/minute, reduce doses by 50%

Alcoholic liver disease. Propylthiouracil has been said to reduce hyperoxic liver injury in hypermetabolic *animals* and despite reports of hepatotoxicity, including some fatalities, associated with propylthiouracil (see Effects on the Liver, under Carbimazole, p.2168), it has been investigated in the treatment of patients with alcoholic liver disease. A systematic review[1], however, concluded that there is no evidence to substantiate this use. Propylthiouracil was associated with adverse effects and it could not be shown to have any significant effects on mortality, liver related mortality, liver complications, and liver histology.

1. Rambaldi A, Gluud C. Propylthiouracil for alcoholic liver disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 01/08/08).

Psoriasis. Several reports have described benefit in patients with psoriasis (p.1583) given propylthiouracil. An oral dose of 300 mg daily for 8 to 12 weeks has been used and is said not to produce clinical hypothyroidism.[1]

1. Elias AN. Anti-thyroid thioureylenes in the treatment of psoriasis. *Med Hypotheses* 2004; **62:** 431–7.

Preparations

BP 2008: Propylthiouracil Tablets;
USP 31: Propylthiouracil Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Prothiucil; ***Braz.:*** Propil; Propilracil; ***Canad.:*** Propyl-Thyracil; ***Cz.:*** Propycil; ***Ger.:*** Propycil; Thyreostat II†; ***Gr.:*** Prothuril; ***Hong Kong:*** CP-PTU; ***Hung.:*** Propycil; ***Israel:*** Propylthiocil; ***Pol.:*** Thyrosan; ***Port.:*** Propycil; ***Swed.:*** Tiotil; ***Switz.:*** Propycil; ***Thai.:*** Propyl; Uracil; ***Turk.:*** Propycil.

Protirelin *(BAN, USAN, rINN)*

Abbott-38579; Lopremone; Protireliini; Protirelina; Protirelinas; Protiréline; Protirelinum; Synthetic TRH; Thyrotrophin-releasing Hormone; Thyrotropin-releasing Hormone; TRF; TRH. L-Pyroglutamyl-L-histidyl-L-prolinamide; 1-[*N*-(5-Oxo-L-prolyl)-L-histidyl]-L-prolinamide; Glu-His-Pro-NH_2.

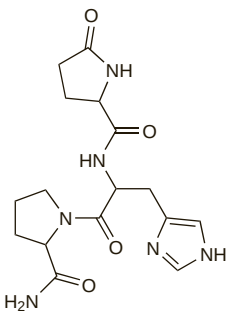
Протирелин

$C_{16}H_{22}N_6O_4$ = 362.4.

CAS — 24305-27-9.

ATC — V04CJ02.

ATC Vet — QV04CJ02.



Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn*, which also includes the tartrate.
Ph. Eur. 6.2 (Protirelin). A synthetic tripeptide with the same sequence of amino acids as the natural hypothalamic neurohormone, that stimulates the release and synthesis of thyrotrophin.