otepa eye drops. As with other alkylating agents, thiotepa is potentially mutagenic, teratogenic, and carcinogenic.

Thiotepa should be given with extreme care, if at all, to patients with pre-existing impairment of hepatic, renal, or bone-marrow function.

Pharmacokinetics

The absorption of thiotepa from the gastrointestinal tract is incomplete and unreliable; variable absorption also occurs from intramuscular injection sites. Absorption through serous membranes such as the bladder and pleura occurs to some extent. After intravenous doses it is rapidly cleared from plasma, with an elimination half-life of about 2.4 hours. It is extensively metabolised: triethylenephosphoramide (TEPA), the primary metabolite, and some of the other metabolites have cytotoxic activity and are eliminated more slowly than the parent compound. It is excreted in the urine: less than 2% of a dose is reported to be present as unchanged drug or its primary metabolite.

Uses and Administration

Thiotepa is an ethyleneimine compound whose antineoplastic effect is related to its alkylating action. It has generally been replaced by cyclophosphamide (p.703) or other drugs. It is not a vesicant and may be given by all parenteral routes, as well as directly into tumour masses.

Instillations of thiotepa may be used in the adjuvant treatment of superficial tumours of the bladder (p.659) and in the control of malignant effusions (p.659). It has been given parenterally in the palliative treatment of various solid tumours, including those of breast and ovary (p.661 and p.670). It has also been given intrathecally to patients with malignant meningeal disease, and has been used, in the form of eye drops, as an adjunct to the surgical removal of pterygium, to prevent recurrence (see p.753).

Thiotepa is given in a variety of dosage schedules. In general, initial doses to suit the individual patient are followed by maintenance doses given at intervals of 1 to 4 weeks. Blood counts are recommended before and during therapy and should continue for at least 3 weeks after stopping. Thiotepa should not be given if the white cell or platelet counts fall below acceptable levels (see also Bone-marrow Depression, p.639) and treatment should be stopped if the white cell count falls rapidly. Dosage should be reduced in patients with lesser degrees of leucopenia.

In the treatment of bladder cancer thiotepa in doses up to 60 mg may be instilled in 30 to 60 mL of sterile water or sodium chloride 0.9% into the bladder of a patient previously dehydrated for 8 to 12 hours, and retained if possible for 2 hours. The instillation may be repeated weekly for up to 4 weeks. Similar instillations have been given at intervals of 1 to 2 weeks, for up to 8 instillations in the prophylaxis of recurrence after surgical removal of bladder cancer. Single doses of 90 mg in 100 mL of sterile water have also been used prophylactically. For malignant effusions, doses of up to 60 mg of thiotepa in 20 to 60 mL of sterile water may be instilled after aspiration; in the USA the licensed dose is 600 to 800 micrograms/kg, a dose similar to that suggested for injection directly into tumours. Thiotepa for local use may be mixed with solutions of procaine and adrenaline.

Intramuscular and intravenous dosage regimens vary considerably; several regimens have used courses of 15 mg daily for 4 days. In the USA a licensed dose is 300 to 400 micrograms/kg given at 1- to 4-week intervals. A solution containing 1 mg/mL in sterile water has been tried intrathecally in doses of up to 10 mg given on alternate days, for up to 4 doses.

Thiotepa 0.05% in sterile Ringer's solution has been instilled as eye drops every 3 hours for up to 6 weeks after surgical removal of pterygium in order to reduce the likelihood of recurrence.

A dose of 60 mg weekly has been instilled into the urethra for the treatment of condylomata acuminata (genital warts). Topical application of thiotepa has also been used for condylomata.

Thiotepa is under investigation for use as conditioning therapy before haematopoietic stem cell transplantation.

Preparations

BP 2008: Thiotepa Injection;
USP 31: Thiotepa for Injection.

Proprietary Preparations (details are given in Part 3)
Gr.: Ledertepa†; ***Ital.:*** Thioplex; ***Neth.:*** Ledertepa; ***Spain:*** Onco Tiotepa†; ***USA:*** Thioplex.

Tioguanine *(BAN, rINN)*

NSC-752; 6-TG; Thioguanine *(USAN)*; 6-Thioguanine; Tioguaniini; Tioguanin; Tioguanina; Tioguaninum; WR-1141. 2-Aminopurine-6(1*H*)-thione; 2-Amino-6-mercaptopurine; 2-Aminopurine-6-thiol.

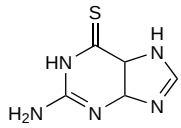
Тиогуанин

$C_5H_5N_5S$ = 167.2.

CAS — 154-42-7 (anhydrous tioguanine); 5580-03-0 (tioguanine hemihydrate).

ATC — L01BB03.

ATC Vet — QL01BB03.



Pharmacopoeias. In *Br.*, *Chin.*, and *US.*
BP 2008 (Tioguanine). A pale yellow, crystalline powder. Practically insoluble in water, in alcohol, and in chloroform; dissolves in dilute solutions of alkali hydroxides.
USP 31 (Thioguanine). It is anhydrous or contains one-half molecule of water of hydration. A pale yellow, odourless or practically odourless, crystalline powder. Insoluble in water and in chloroform; soluble 1 in 7700 of alcohol; freely soluble in dilute solutions of alkali hydroxides. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Mercaptopurine, p.744.

In some patients, gastrointestinal reactions are reported to be less frequent than with mercaptopurine.

Effects on the blood. For the view that it may be possible to predict those individuals likely to have severe bone-marrow depression with tioguanine based on measurement of the activity of thiopurine methyltransferase or the concentration of tioguanine nucleotide, see under Azathioprine, p.1819.

Effects on the liver. The use of tioguanine has been limited by reports of hepatic veno-occlusive disease attributed to the drug.[1-4] The manufacturer (*GlaxoSmithKline*) has stated that, in most cases, liver toxicity is reversible upon withdrawal of chemotherapy. A comparison with mercaptopurine in the maintenance treatment of children with acute lymphoblastic leukaemia found that of 95 patients who developed veno-occlusive disease, 82 were receiving tioguanine, representing about 11% of all patients assigned to the drug.[5] In addition, although tioguanine was associated with fewer CNS relapses, patients in the tioguanine arm were more likely to develop fatal infections.

Centrilobular hepatic necrosis has also been reported; reports are confounded by the use of high doses of tioguanine, other antineoplastics, oral contraceptives, and chronic alcohol abuse.

1. Gill RA, *et al.* Hepatic veno-occlusive disease caused by 6-thioguanine. *Ann Intern Med* 1982; **96:** 58–60.
2. Krivoy N, *et al.* Reversible hepatic veno-occlusive disease and 6-thioguanine. *Ann Intern Med* 1982; **96:** 788.
3. Kao NL, Rosenblate HJ. 6-Thioguanine therapy for psoriasis causing toxic hepatic venoocclusive disease. *J Am Acad Dermatol* 1993; **28:** 1017–18.
4. Romagosa R, *et al.* Treatment of psoriasis with 6-thioguanine and hepatic venoocclusive disease. *J Am Acad Dermatol* 2002; **47:** 970–2.
5. Vora A, *et al.* Medical Research Council/National Cancer Research Network Childhood Leukaemia Working Party. Toxicity and efficacy of 6-thioguanine versus 6-mercaptopurine in childhood lymphoblastic leukaemia: a randomised trial. *Lancet* 2006; **368:** 1339–48.

Handling and disposal. For reference to a method for the destruction of tioguanine in wastes, see Mercaptopurine, p.744.

Interactions

Unlike mercaptopurine (p.744), normal doses of tioguanine may be used with allopurinol.

A number of cases of portal hypertension with hepatic nodular regenerative hyperplasia have been reported in patients who received tioguanine with busulfan (see p.691).

It has been suggested that daunorubicin might enhance the hepatotoxicity of tioguanine (see p.709).

Pharmacokinetics

Tioguanine is incompletely and variably absorbed from the gastrointestinal tract; on average about 30% of a dose is absorbed after oral doses. It is rapidly activated in the body by intracellular conversion to its nucleotide, thioguanylic acid and its thioguanosine phosphate derivatives. With repeated doses increasing amounts of the nucleotide are incorporated into DNA. Very little unchanged tioguanine has been detected circulating in the blood but the half-life of the nucleotide in the tissues is prolonged. Tioguanine is inactivated primarily by methylation to aminomethylthiopurine; small amounts are deaminated to thioxanthine, and may go on to be oxidised by xanthine oxidase to thiouric acid, but inactivation is essentially independent of xanthine oxidase and is not affected by inhibition of the enzyme.

It is excreted in the urine almost entirely as metabolites; only negligible amounts of tioguanine have been detected. Tioguanine does not appear to cross the blood-brain barrier to a significant extent; very little is found in CSF after normal clinical doses. It crosses the placenta.

Uses and Administration

Tioguanine is an analogue of the naturally occurring purine, guanine, and is an antineoplastic with actions and uses similar to those of mercaptopurine (p.744). It appears to cause fewer gastrointestinal reactions but cross-resistance exists so that patients who do not respond to one are unlikely to respond to the other.

Tioguanine may be given orally, usually with other antineoplastics, in the induction of remissions in acute myeloid leukaemia (p.652). It has also been used in other malignancies including acute lymphoblastic leukaemia (p.651) and chronic myeloid leukaemia (p.653).

Doses of between 100 and 200 mg/m^2 daily have been given at various stages of treatment for short term cycles; similar doses have been used in children. A dose of 2 mg/kg daily increased after 4 weeks, if there is no response or toxicity allows, to 3 mg/kg daily may be given to adults and children in those rare cases when single agent therapy is considered appropriate.

Blood counts should be made frequently, particularly during induction and when tioguanine is given with other antineoplastics. Therapy should be withdrawn at the first sign of severe bone-marrow depression. Tioguanine is not recommended for long-term continuous therapy because of the high risk of hepatotoxicity (see Effects on the Liver, above).

Tioguanine has been given intravenously as the sodium salt.

Psoriasis. A report of the use of tioguanine, in doses ranging from 20 mg twice weekly to 120 mg daily, in the management of patients with refractory psoriasis.[1] Dramatic improvement occurred in 14 of 18 patients, but a further 2 were unable to tolerate the drug. Myelosuppression was the principal toxic effect and it was suggested that thiopurine methyltransferase activity could be measured as a basis to determine initial dosage and the risk of toxicity. For the conventional management of psoriasis see p.1583.

1. Mason C, Krueger GG. Thioguanine for refractory psoriasis. *J Am Acad Dermatol* 2001; **44:** 67–72.

Preparations

BP 2008: Tioguanine Tablets;
USP 31: Thioguanine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Lanvis; ***Austral.:*** Lanvis; ***Belg.:*** Lanvis; ***Braz.:*** Lanvis; ***Canad.:*** Lanvis; ***Chile:*** Lanvis; ***Cz.:*** Lanvis; ***Fr.:*** Lanvis; ***Gr.:*** Lanvis; ***Hong Kong:*** Lanvis; ***Irl.:*** Lanvis; ***Israel:*** Lanvis; ***Malaysia:*** Lanvis; ***Neth.:*** Lanvis; ***NZ:*** Lanvis; ***Pol.:*** Lanvis; ***S.Afr.:*** Lanvis; ***Singapore:*** Lanvis†; ***Swed.:*** Lanvis; ***Switz.:*** Lanvis; ***Thai.:*** Lanvis; ***UK:*** Lanvis; ***USA:*** Tabloid.

Tipifarnib *(USAN, rINN)*

R-115777; Tipifarnibum. (+)-6-[(*R*)-Amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone.

Типифарниб

$C_{27}H_{22}Cl_2N_4O$ = 489.4.

CAS — 192185-72-1.