Uses and Administration

Sulfinpyrazone is a uricosuric drug used to treat hyperuricaemia associated with chronic gout (p.552). It also has some antiplatelet activity.

Sulfinpyrazone is used in chronic gout to inhibit the renal tubular reabsorption of uric acid so increasing the urinary excretion of uric acid, lowering plasma-urate concentrations, and eventually reducing urate deposits in the tissues. It is therefore of value in hyperuricaemia caused by decreased uric acid excretion rather than increased urate production and is not used for hyperuricaemia associated with cancer or cancer therapy.

Sulfinpyrazone has little analgesic or anti-inflammatory action and is of no value in acute gout. Initially, it may increase plasma concentrations of urate and uric acid by dissolving deposits. This can trigger or exacerbate acute attacks, hence sulfinpyrazone should not be given until an acute attack has completely subsided, and an NSAID or colchicine may be given during the first few months.

The initial oral dose of sulfinpyrazone in the UK is 100 to 200 mg daily (the USA allows up to 200 mg twice daily), taken with meals or milk. This may be gradually increased over 1 to 3 weeks until a daily dosage of 600 mg is reached; up to 800 mg daily may be given if necessary. After the plasma-urate concentration has been controlled, the daily maintenance dose may be reduced to as low as 200 mg. An adequate fluid intake is required to prevent formation of uric acid renal calculi.

Antiplatelet therapy. Sulfinpyrazone inhibits platelet function, thereby inhibiting thrombosis. A meta-analysis of studies, conducted by the Antiplatelet Trialists' Collaboration, has shown that it reduces the risk of myocardial infarction, stroke, or vascular death in patients at high risk of occlusive vascular disease[1] and also reduces the risk of occlusion in patients undergoing arterial reperfusion and revascularisation procedures.[2] However, aspirin is the most widely used antiplatelet therapy, as discussed under Cardiovascular Risk Reduction, on p.1164.

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; **308:** 81–106.
2. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—II: maintenance of vascular graft or arterial patency by antiplatelet therapy. *BMJ* 1994; **308:** 159–68.

Preparations

BP 2008: Sulfinpyrazone Tablets;
USP 31: Sulfinpyrazone Capsules; Sulfinpyrazone Tablets.

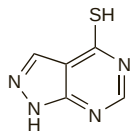
Proprietary Preparations (details are given in Part 3)
Ital.: Enturen; ***Port.:*** Sulfinona†; ***UK:*** Anturan; ***USA:*** Anturane.

Tisopurine *(rINN)*

MPP; Thioallopurinol; Thiopurinol; Tisopurina; Tisopurinum. 1*H*-Pyrazolo[3,4-*d*]pyrimidine-4-thiol.

Тизопурин

$C_5H_4N_4S$ = 152.2.
CAS — 5334-23-6.
ATC — M04AA02.
ATC Vet — QM04AA02.



Profile

Tisopurine, an analogue of allopurinol, is an inhibitor of uric acid synthesis. It is used orally in the treatment of disorders associated with hyperuricaemia (p.552), including gout, in doses of 100 to 400 mg daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Exuracid.

Urate Oxidase

CB-8129; Uricasa; Uricase.

Уратоксидаза
CAS — 9002-12-4.
ATC — M04AX01.
ATC Vet — QM04AX01.

Rasburicase *(BAN, USAN, rINN)*

Rasburicasa; Rasburicasum; Rasburikaasi; Rasburikas; Rasburikaz; SR-29142.

Разбуриказа
CAS — 134774-45-1.
ATC — V03AF07.
ATC Vet — QV03AF07.

Description. Rasburicase is a recombinant form of the enzyme urate oxidase.

Adverse Effects

The most serious adverse effects of rasburicase involve hypersensitivity reactions, including anaphylaxis, rashes, bronchospasm, rhinitis, urticaria, hypotension, dyspnoea, and chest pain and tightness. Haemolysis and methaemoglobinaemia have also been reported. Other adverse effects are nausea, vomiting, abdominal pain, constipation, diarrhoea, headache, fever, respiratory distress, sepsis, neutropenia, and mucositis.

Precautions

Treatment with rasburicase should be immediately and permanently stopped if hypersensitivity reactions, methaemoglobinaemia, or haemolysis develop. Rasburicase is contra-indicated in patients with G6PD deficiency or other cellular metabolic disorders known to cause haemolytic anaemia; hydrogen peroxide, which is produced during oxidation of uric acid to allantoin, can induce haemolytic anaemia in these patients. Patients at higher risk of having G6PD deficiency should be screened before receiving rasburicase.

Uses and Administration

Rasburicase is a recombinant form of the enzyme urate oxidase, which oxidises uric acid to allantoin. It is used in the treatment and prophylaxis of severe hyperuricaemia (p.552) associated with the treatment of malignancy. It is given by intravenous infusion before and during the start of chemotherapy, in a dose of 150 or 200 micrograms/kg daily over 30 minutes. Duration of treatment may vary from 5 to 7 days.

The native form of urate oxidase has also been used.

Gout. Rasburicase has been used successfully to treat gout in patients allergic to allopurinol.[1,2]

1. Vogt B. Urate oxidase (rasburicase) for treatment of severe tophaceous gout. *Nephrol Dial Transplant* 2005; **20:** 431–3.
2. Richette P, Bardin T. Successful treatment with rasburicase of a tophaceous gout in a patient allergic to allopurinol. *Nat Clin Pract Rheumatol* 2006; **2:** 338–42.

Tumour lysis syndrome. The tumour lysis syndrome (p.639) represents a biochemical disturbance after massive release of cellular breakdown products from tumour cells sensitive to therapy; hyperuricaemia is a cardinal feature. Rasburicase was effective in the prophylaxis or treatment of hyperuricaemia in children and young adults with leukaemia or lymphoma who either presented with abnormally high plasma concentrations of uric acid or had large tumour cell burdens.[1] Treatment was mostly well tolerated; one patient developed nausea and vomiting and one experienced bronchospasm and hypoxaemia 3 hours after infusion. Antibodies to rasburicase were seen in 17 of 121 assessable patients. Safety and efficacy were confirmed in further studies of children[2] and adults[2,3] considered to be at particularly high risk of tumour lysis syndrome. In children[4] with haematologic malignancies at high risk for tumour lysis, rasburicase given intravenously achieved more rapid control and lower levels of plasma uric acid than oral allopurinol. No antibodies to rasburicase were detected at day 14. In 3 children with acute lymphoblastic leukaemia, hyperuricaemia was reportedly controlled with oral allopurinol and a single dose of rasburicase, although subclinical tumour lysis was apparent.[5] Rasburicase has also been used for tumour lysis syndrome in neonates. One infant was given a single dose of rasburicase after 2 days of induction chemotherapy for neuroblastoma, started on day 21 of life; serum urate normalised and chemotherapy was completed without further incident. A second infant, with acute lymphoblastic leukaemia and renal dysfunction, presented with tumour lysis syndrome, and had 6 doses of intravenous rasburicase plus aggressive supportive therapy, but died of complications on day 7 of life.[6] Reviews[7,8] have concluded that rasburicase is highly effective at decreasing uric acid concentrations rapidly and thoroughly; there is some suggestion that shorter durations of treatment (between 1 and 3 days as opposed to 5 days) may be sufficient even in high-risk patients.

1. Pui C-H, *et al.* Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients with leukaemia or lymphoma. *J Clin Oncol* 2001; **19:** 697–704.
2. Pui C-H, *et al.* Recombinant urate oxidase (rasburicase) in the prevention and treatment of malignancy-associated hyperuricemia in pediatric and adult patients: results of a compassionate-use trial. *Leukemia* 2001; **15:** 1505–9.
3. Coiffier B, *et al.* Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma) study. *J Clin Oncol* 2003; **21:** 4402–6.
4. Goldman SC, *et al.* A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. *Blood* 2001; **97:** 2998–3003.
5. Lee ACW, *et al.* Treatment of impending tumor lysis with single-dose rasburicase. *Ann Pharmacother* 2003; **37:** 1614–17.
6. McNutt DM, *et al.* Rasburicase for the management of tumor lysis syndrome in neonates. *Ann Pharmacother* 2006; **40:** 1445–50.
7. Bessmertny O, *et al.* Rasburicase: a new approach for preventing and/or treating tumor lysis syndrome. *Curr Pharm Des* 2005; **11:** 4177–85.
8. Oldfield V, Perry CM. Rasburicase: a review of its use in the management of anticancer therapy-induced hyperuricaemia. *Drugs* 2006; **66:** 529–45.

Preparations

Proprietary Preparations (details are given in Part 3)

Austral.: Fasturtec; ***Belg.:*** Fasturtec; ***Braz.:*** Fasturtec; ***Canad.:*** Fasturtec; ***Chile:*** Fasturtec†; ***Cz.:*** Fasturtec; ***Denm.:*** Fasturtec; ***Fin.:*** Fasturtec; ***Fr.:*** Fasturtec; ***Ger.:*** Fasturtec; ***Gr.:*** Fasturtec; ***Hong Kong:*** Fasturtec; ***Hung.:*** Fasturtec; ***Irl.:*** Fasturtec; ***Ital.:*** Fasturtec; Uricozyme†; ***Neth.:*** Fasturtec; ***Norw.:*** Fasturtec; ***NZ:*** Fasturtec; ***Pol.:*** Fasturtec; ***Port.:*** Fasturtec; ***Singapore:*** Fasturtec; ***Spain:*** Fasturtec; ***Swed.:*** Fasturtec; ***Switz.:*** Fasturtec; ***UK:*** Fasturtec; ***USA:*** Elitek; ***Venez.:*** Fasturtec.

effective, especially in the elderly, in whom the inappropriate prescribing of drugs for postural instability needs to be avoided. Such measures include improving visual acuity, balance exercises, and the use of walking aids.

The most widely used drugs for acute vertigo are the antihistamines. They may have a direct action on the inner ear besides acting centrally. Antimuscarinic actions may contribute to their activity; antimuscarinics, especially hyoscine, have a long history of use in vertigo. Antihistamines used in the treatment of vertigo include buclizine, cyclizine, dimenhydrinate, diphenhydramine, meclozine, and promethazine. Cinnarizine and flunarizine are also used for vertigo although they are devoid of any significant antimuscarinic actions; their activity may be due to calcium-channel blockade. Phenothiazines such as prochlorperazine are also used to control any associated vomiting. Benzodiazepines including diazepam have been given in acute severe attacks. However their prolonged use in those with chronic symptoms is of questionable value.

Vasodilators may be of benefit in the treatment of vertigo of vascular aetiology. Parenteral or sublingual histamine was formerly widely used, and betahistine is still advocated especially for vertigo associated with Ménière's disease. Nicotinyl alcohol has also been used.

References.

1. Rascol O, *et al.* Antivertigo medications and drug-induced vertigo: a pharmacological review. *Drugs* 1995; **50:** 777–91.
2. Luxon LM. Vertigo: new approaches to diagnosis and management. *Br J Hosp Med* 1996; **56:** 519–20 and 537–41.
3. Luxon LM. Assessment and management of vertigo. *Prescribers' J* 1998; **38:** 87–97.
4. Baloh RW. Vertigo. *Lancet* 1998; **352:** 1841–6.
5. Hain TC, Uddin M. Pharmacological treatment of vertigo. *CNS Drugs* 2003; **17:** 85–100.

Acrivastine *(BAN, USAN, rINN)*

Acrivastin; Acrivastina; Acrivastinum; Akrivastiini; Akrivastin; BW-825C. (*E*)-3-{6-[(*E*)-3-Pyrrolidin-1-yl-1-*p*-tolylprop-1-enyl]-2-pyridyl}acrylic acid.

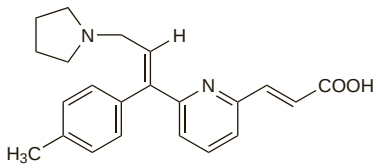
Акривастин

$C_{22}H_{24}N_2O_2$ = 348.4.

CAS — 87848-99-5.

ATC — R06AX18.

ATC Vet — QR06AX18.



Adverse Effects and Precautions

As for the non-sedating antihistamines in general, p.561. Acrivastine should be given with care in renal impairment; UK licensed product information recommends that it should not be given to patients with significant renal impairment, while product information in other countries, such as Switzerland for example, contra-indicates its use in those with a creatinine clearance of less than 50 mL/minute. Acrivastine should not be used in patients hypersensitive to triprolidine.

Sedation. For a discussion of the sedative effects of antihistamines see p.562.

Interactions

As for the non-sedating antihistamines in general, p.563.

Pharmacokinetics

Acrivastine is well absorbed from the gastrointestinal tract; peak plasma concentrations are achieved in about 1.5 hours. The plasma half-life of acrivastine is about 1.5 hours and the drug does not appear to cross the blood-brain barrier to a significant extent. Acrivastine along with an active metabolite is excreted principally in the urine.

Uses and Administration

Acrivastine is a non-sedating antihistamine structurally related to triprolidine. It does not have any significant sedative or antimuscarinic actions. It is used for the symptomatic relief of allergic conditions such as rhinitis (p.565) and various types of urticaria (p.565) when it is given in oral doses of 8 mg three times daily. It is also used with a decongestant such as pseudoephedrine hydrochloride.

Administration in renal impairment. See Precautions, above

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Semprex; ***Cz.:*** Semprex†; ***Denm.:*** Benadryl; ***Fin.:*** Benadryl; Semprex†; ***Hong Kong:*** Semprex; ***Ital.:*** Semprex; ***Malaysia:*** Semprex; ***Neth.:*** Semprex; ***Philipp.:*** Semprex; ***Rus.:*** Semprex (Семпрекс); ***S.Afr.:*** Semprex; ***Singapore:*** Semprex; ***Swed.:*** Semprex; ***Switz.:*** Semprex; ***Thai.:*** Semprex†; ***Turk.:*** Semprex; ***UK:*** Benadryl Allergy Relief.

Multi-ingredient: ***Austria:*** Duact; ***Denm.:*** Duact; ***Fin.:*** Duact; ***Turk.:*** Duact; ***UK:*** Benadryl Plus; ***USA:*** Semprex-D.

Alimemazine Tartrate *(BANM, rINNM)*

Alimémazine, Tartrate d'; Alimemazini Tartras; Tartrato de alimemazina; Trimeprazine Tartrate. *NN*-Dimethyl-2-methyl-3-(phenothiazin-10-yl)propylamine tartrate.

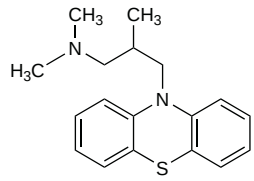
Алимемазина Тартрат

$(C_{18}H_{22}N_2S)_2,C_4H_6O_6$ = 747.0.

CAS — 84-96-8 (alimemazine); 4330-99-8 (alimemazine tartrate).

ATC — R06AD01.

ATC Vet — QR06AD01.



(alimemazine)

Pharmacopoeias. In *Br.*, *Fr.*, *Jpn*, and *US*.

BP 2008 (Alimemazine Tartrate). A white or slightly cream powder. It darkens on exposure to light. Freely soluble in water; sparingly soluble in alcohol; very slightly soluble in ether. A 2% solution in water has a pH of 5.0 to 6.5. Protect from light.

USP 31 (Trimeprazine Tartrate). A white to off-white, odourless, crystalline powder. Soluble 1 in 2 of water, 1 in 20 of alcohol, 1 in 5 of chloroform, and 1 in 1800 of ether; very slightly soluble in benzene. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561.

Children. There have been reports of adverse effects in children given alimemazine tartrate orally. Fatal malignant hyperthermia[1] and severe cardiovascular depression[2] have occurred after its use for premedication, and severe respiratory and CNS depression[3] after use as a postoperative sedative. Doses in these 3 reports ranged from 2.4 to 4.4 mg/kg. Although unconfirmed, a possible association between phenothiazine sedatives and sudden infant death syndrome has also been suggested (see Promethazine Hydrochloride, p.588). Alimemazine tartrate is no longer licensed in the UK for short-term sedation in children and it is recommended that it should not be used in infants less than 2 years of age (but see below). The maximum recommended oral dose for premedication of children aged 2 to 7 years is 2 mg/kg. There has been a warning[4] that the use of alimemazine for deep sedation in diagnostic and therapeutic procedures in children is associated with prolonged drowsiness and that standards of monitoring, starvation, and postprocedural care should be similar to those with general anaesthesia.

1. Moyes DG. Malignant hyperpyrexia caused by trimeprazine. *Br J Anaesth* 1973; **45:** 1163–4.
2. Loan WB, Cuthbert D. Adverse cardiovascular response to oral trimeprazine in children. *BMJ* 1985; **290:** 1548–9.
3. Mann NP. Trimeprazine and respiratory depression. *Arch Dis Child* 1981; **56:** 481–2.
4. Cray SH, Hinton W. Sedation for investigations: prolonged effect of chloral and trimeprazine. *Arch Dis Child* 1994; **71:** 179.

Pregnancy. For a discussion of the use of antihistamines in pregnancy, including studies involving phenothiazines, see p.563.

Interactions

As for the sedating antihistamines in general, p.563.

Uses and Administration

Alimemazine, a phenothiazine derivative, is a sedating antihistamine with antiemetic activity and pronounced sedative effects. It also has some antimuscarinic actions. It is used mainly for the relief of urticaria (p.565) and pruritus (p.565), and, in the UK, for pre-operative medication in children. Alimemazine may also be used in compound preparations for the symptomatic treatment of coughs (p.564).

Alimemazine tartrate is given orally; doses in the UK are given as the amount of alimemazine tartrate, while those in some other countries are expressed in terms of the equivalent amount of alimemazine. Alimemazine tartrate 25 mg is equivalent to about 20 mg of alimemazine.

- The adult dose of alimemazine tartrate used for the relief of **urticaria** and **pruritus** in the *UK* is 10 mg two or three times daily; up to 100 mg daily has been given in refractory cases. Elderly patients are given 10 mg once or twice daily and children over 2 years of age 2.5 to 5 mg three or four times daily. Despite the view that alimemazine should not be given to younger children (see above), and although not licensed in the UK, the *BNFC* suggests that 250 micrograms/kg (maximum of 2.5 mg) three or four times daily may be given to those aged 6 months to 2 years for the relief of urticaria and pruritus, but only under specialist care.
- Doses used in the *USA* have been lower, even allowing for them being expressed in terms of alimemazine. The adult dose was the equivalent of alimemazine 2.5 mg four times daily. Children in the USA 3 years of age and over have been given 2.5 mg at night or three times daily. However, it appears that proprietary preparations are no longer available in the USA.
- The usual recommended dose in the UK for **premedication** in children aged 2 to 7 years is up to 2 mg/kg given about one to two hours before the operation.

Anaesthesia. Alimemazine tartrate may be used for anaesthetic premedication (see p.563) in children if the oral route is preferred to the more usual parenteral route of other phenothiazine antihistamines. Adverse effects have, however, been reported in children (see under Adverse Effects and Precautions, above), and in the UK alimemazine tartrate is not licensed for use in infants less than 2 years of age.

Insomnia. Antihistamines such as alimemazine tartrate have been used as alternatives to benzodiazepines for the short-term treatment of insomnia (p.564), particularly for children. However, their antimuscarinic side-effects may prove troublesome.

Regimens involving a short course of alimemazine tartrate in high dosage were tried in order to alter the sleep pattern of children with sleeping difficulties.[1,2] Adverse effects have, however, been reported in children (see under Adverse Effects and Precautions, above). The UK product is no longer indicated for short-term sedation in children and should not be used in infants less than 2 years of age.

1. Valman HB. ABC of 1 to 7 (revised): sleep problems. *BMJ* 1987; **294:** 828–30.
2. Anonymous. What can be done for night waking in children? *Lancet* 1987; **ii:** 948–9.

Preparations

BP 2008: Alimemazine Tablets; Paediatric Alimemazine Oral Solution; Strong Paediatric Alimemazine Oral Solution;
USP 31: Trimeprazine Tartrate Syrup; Trimeprazine Tartrate Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Chemists Own Peetalix†; Vallergan; ***Belg.:*** Theralene; ***Canad.:*** Panectyl; ***Fr.:*** Theralene; ***Ger.:*** Repeltin†; ***Irl.:*** Vallergan; ***Neth.:*** Nedeltran; ***Norw.:*** Vallergan; ***NZ:*** Vallergan; ***S.Afr.:*** Vallergan; ***Spain:*** Variargil; ***Swed.:*** Theralen; ***UK:*** Vallergan.

Multi-ingredient: ***Fr.:*** Sirop Teyssedre; Theralene Pectoral Nourrisson†.