Reducing the urinary concentration of some drugs could diminish their activity in certain diseases as might happen with nitrofurantoin or some quinolones in urinary-tract infections and penicillamine in cystinuria.

Allopurinol. Probenecid may increase the clearance of allopurinol despite an increased hypouricaemic effect when these 2 drugs are given together (see Antigout Drugs, under Allopurinol, p.553).

Pharmacokinetics

Probenecid is completely absorbed from the gastrointestinal tract with peak plasma concentrations achieved 2 to 4 hours after a dose. It is extensively bound to plasma proteins (85 to 95%). The plasma half-life is dose-dependent and ranges from less than 5 to more than 8 hours. Probenecid crosses the placenta. It is metabolised by the liver, and excreted in the urine mainly as metabolites. Excretion of unchanged probenecid is increased in alkaline urine.

Uses and Administration

Probenecid is a uricosuric drug used to treat hyperuricaemia (p.552) associated with chronic gout; it has also been used to treat hyperuricaemia caused by diuretic therapy. It is also used as an adjunct to some antibacterials to reduce their renal tubular excretion and is given with the antiviral cidofovir to reduce nephrotoxicity.

Probenecid is used in **chronic gout and hyperuricaemia** 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. Probenecid 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.

Probenecid has no 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 probenecid should not be started until an acute attack has completely subsided, and an NSAID or colchicine may be given during the first few months.

It is usual to start treatment for gout with oral doses of 250 mg twice daily increased after a week to 500 mg twice daily and later, if the therapeutic effects are inadequate, by increments of 500 mg every 4 weeks, up to 2 g daily. Probenecid may not be effective in chronic renal impairment particularly when the glomerular filtration rate is less than 30 mL/minute. An adequate fluid intake is required to reduce the risk of uric acid renal calculi.

When the patient has been free from acute attacks for at least 6 months, and provided that the plasma-urate concentration is within acceptable limits, the daily dose may be gradually reduced, by 500 mg every 6 months, to the lowest effective maintenance dose which is then given indefinitely.

Probenecid may also be used as an **adjunct to antibacterial therapy** particularly when treating severe or resistant infections. It reduces the tubular excretion of penicillins and most cephalosporins and may increase their plasma concentrations up to fourfold. The usual dosage for reducing tubular excretion of penicillins and cephalosporins is 500 mg four times daily, or less in elderly patients with suspected renal impairment. When renal impairment is sufficient to retard the excretion of antibacterials, probenecid should not be given.

The dosage for children over 2 years of age and weighing less than 50 kg is 25 mg/kg (700 mg/m^2) initially, followed by 10 mg/kg (300 mg/m^2) every 6 hours.

Single oral doses of probenecid 1 g are given with a suitable oral antibacterial, or at least 30 minutes before an injected antibacterial, in the single-dose treatment of gonorrhoea (p.191).

Doses of probenecid to be used with cidofovir are given on p.868.

Preparations

BP 2008: Probenecid Tablets;
USP 31: Ampicillin and Probenecid for Oral Suspension; Probenecid and Colchicine Tablets; Probenecid Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Pro-Cid; ***Canad.:*** Benuryl; ***Fin.:*** Probecid†; ***Fr.:*** Benemide; ***Gr.:*** Benemid; ***India:*** Bencid; ***Mex.:*** Benecid; ***Norw.:*** Probecid; ***S.Afr.:*** Proben; ***Swed.:*** Probecid; ***Thai.:*** Benacid; Bencid; Benemid†; ***USA:*** Benemid.

Multi-ingredient: ***USA:*** ColBenemid.

Used as an adjunct in: ***Braz.:*** Emicilin; Gonol; ***Spain:*** Blenox.

Sulfinpyrazone *(BAN, rINN)*

G-28315; Sulfinpirazona; Sulfinpirazonas; Sulfinpyratsoni; Sulfinpyrazon; Sulfinpyrazonum; Sulphinpyrazone; Sulphoxyphenylpyrazolidine; Szulfinpirazon. 1,2-Diphenyl-4-(2-phenylsulphinylethyl)pyrazolidine-3,5-dione.

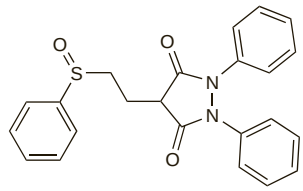
Сульфинпиразон

$C_{23}H_{20}N_2O_3S$ = 404.5.

CAS — 57-96-5.

ATC — M04AB02.

ATC Vet — QM04AB02.



Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US.*
Ph. Eur. 6.2 (Sulfinpyrazone). A white or almost white powder. Very slightly soluble in water; sparingly soluble in alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.
USP 31 (Sulfinpyrazone). A white to off-white powder. Practically insoluble in water and in petroleum spirit; soluble in alcohol and in acetone; sparingly soluble in dilute alkali.

Adverse Effects and Treatment

The most frequent adverse effects of sulfinpyrazone involve the gastrointestinal tract, and include nausea, vomiting, diarrhoea and abdominal pain. It may cause gastric bleeding or aggravate existing peptic ulcers. Skin rashes have been reported, and may be associated with a hypersensitivity reaction. Aplastic anaemia, agranulocytosis, leucopenia, and thrombocytopenia have been reported rarely as have raised liver enzyme values, jaundice, and hepatitis, renal impairment, salt and water retention, and acute renal failure.

When used in chronic gout, particularly during the first few months of treatment, sulfinpyrazone may precipitate acute attacks and there is a risk of uric acid renal calculi developing.

Symptoms of overdosage include hypotension, acute renal failure, arrhythmias, respiratory disorders, convulsions, and coma, as well as gastrointestinal effects. Treatment of overdose may involve activated charcoal if a substantial amount has been ingested within 1 hour of presentation, followed by symptomatic and supportive therapy.

Effects on the kidneys. Although renal failure has been reported occasionally in patients receiving sulfinpyrazone for gout[1] many of the cases have occurred in those given the drug for myocardial infarction.[2,3] Acute renal failure may also occur after overdose or in patients with intravascular volume depletion.[4,5]

1. Durham DS, Ibels LS. Sulphinpyrazone-induced acute renal failure. *BMJ* 1981; **282:** 609.
2. Boelaert J, *et al.* Sulphinpyrazone-induced decrease in renal function: a review of reports with discussion of pathogenesis. *Acta Clin Belg* 1982; **37:** 368–75.
3. Lijnen P, *et al.* Decrease in renal function due to sulphinpyrazone treatment early after myocardial infarction. *Clin Nephrol* 1983; **19:** 143–6.
4. Florkowski CM, *et al.* Acute non-oliguric renal failure secondary to sulphinpyrazone overdose. *J Clin Pharm Ther* 1992; **17:** 71.
5. Walls M, *et al.* Acute renal failure due to sulfinpyrazone. *Am J Med Sci* 1998; **315:** 319–21.

Precautions

Sulfinpyrazone should not be started during an acute attack of gout; however, treatment is usually continued when acute attacks occur in patients already receiving the drug, and the acute attack is treated separately. Sulfinpyrazone is not suitable for the control of hyperuricaemia associated with cancer or cancer chemotherapy.

Sulfinpyrazone should be given with care to patients with renal impairment or heart failure and is contra-indicated in those with severe renal or hepatic impairment. It is also contra-indicated in patients with blood dyscrasias or blood coagulation disorders, and in patients with uric acid renal calculi or peptic ulcer disease or a history of such disorders.

Sulfinpyrazone should not be given to patients hypersensitive to it or to other pyrazole derivatives such as phenylbutazone; nor should it be given to patients in whom hypersensitivity reactions (including bronchospastic reactions in asthmatics) have been provoked by aspirin or by other drugs with prostaglandin-synthetase inhibiting activity.

To reduce the risk of uric acid renal calculi an adequate fluid intake (2 to 3 litres daily) is required; alkalinising the urine with sodium bicarbonate or potassium citrate may also be considered. It is recommended that patients have periodic full blood counts to detect any haematological abnormalities.

Renal-function tests involving aminohippuric acid or phenolsulfonphthalein may be invalidated.

Porphyria. Sulfinpyrazone is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

Doses of sulfinpyrazone may need to be increased if it is given with other drugs, such as diuretics or pyrazinamide, that increase uric acid concentrations. Sulfinpyrazone and salicylates including aspirin are mutually antagonistic and should not be used together. There may also be an increased risk of bleeding when sulfinpyrazone is used with other drugs such as aspirin that inhibit platelet function.

Sulfinpyrazone's renal tubular secretion is inhibited by probenecid although with little clinical effect. Since sulfinpyrazone, like probenecid, inhibits the tubular secretion of weak organic acids, interactions can be expected with penicillins although the effect is not considered to be clinically useful.

Sulfinpyrazone can potentiate the action of some drugs. The most significant interaction of this type involves warfarin, acenocoumarol, and possibly other coumarin anticoagulants (p.1429). Patients receiving sulfinpyrazone and such an anticoagulant should have their prothrombin times monitored and the anticoagulant dosage reduced as appropriate. Similarly, sulfinpyrazone may potentiate the effects of phenytoin (see Antigout Drugs, p.499), and possibly some sulfonamides and sulfonylureas.

In contrast, sulfinpyrazone may increase the metabolism of theophylline (p.1144) and diminish its activity.

Pharmacokinetics

Sulfinpyrazone is readily absorbed from the gastrointestinal tract. It is about 98% bound to plasma proteins and has a plasma half-life of about 2 to 4 hours. Sulfinpyrazone is partly metabolised in the liver and some of the metabolites are active. On long-term therapy, sulfinpyrazone induces its own metabolism. Unchanged drug and metabolites are mainly excreted in the urine.

◊ References.

1. Bradbrook ID, *et al.* Pharmacokinetics of single doses of sulphinpyrazone and its major metabolites in plasma and urine. *Br J Clin Pharmacol* 1982; **13:** 177–85.
2. Schlicht F, *et al.* Pharmacokinetics of sulphinpyrazone and its major metabolites after a single dose and during chronic treatment. *Eur J Clin Pharmacol* 1985; **28:** 97–103.

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.

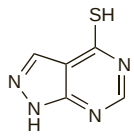
Proprietary Preparations (details are given in Part 3)
Ital.: Enturen; ***Port.:*** Sulfinona†; ***UK:*** Anturan; ***USA:*** Anturane.

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.