(ANC <1500 cells/mm$^3$) is rare. Licensed product information recommends that neutrophil counts should be taken before starting anakinra and periodically throughout treatment. UK licensed information recommends monthly monitoring during the first 6 months and then quarterly thereafter; US licensed information requires monthly monitoring for the first 3 months and then quarterly monitoring for a period of up to 1 year. Anakinra should not be started in patients with neutropenia. Small reductions in the total white blood cell and platelets counts and a small increase in eosinophils have also been noted. Anakinra is also associated with an increased incidence of lymphoma in patients with rheumatoid arthritis.

For caution in patients with renal impairment see under Uses and Administration, below.

**Effects on the cardiovascular system.** A 29-year-old woman with refractory adult-onset Still's disease developed shortness of breath, which progressed to cardiorespiratory failure, 3 months after being started on anakinra;[1] although resuscitation was tried, the patient died. The authors considered that the role of anakinra in this event was unclear, particularly as the patient had shown some evidence of myocardial or pulmonary dysfunction before starting the drug.

1. Ruiz PJ, *et al.* Cardiac death in a patient with adult-onset Still's disease treated with the interleukin 1 receptor inhibitor anakinra. *Ann Rheum Dis* 2007; **66:** 422–3.

**Effects on the skin.** Inflammatory lesions at injection sites were reported in 5 patients after anakinra use.[1] The lesions were erythematous, oedematous, painful, and itchy plaques, and were seen within 16 days of starting treatment. Treatment with anakinra was completely stopped in 1 patient and interrupted in 2 other patients; when reintroduced, one patient developed abdominal pain, dyspnoea, and facial and abdominal erythema with pruritus.

1. Vila AT, *et al.* Adverse cutaneous reactions to anakinra in patients with rheumatoid arthritis: clinicopathological study of five patients. *Br J Dermatol* 2005; **153:** 417–23.

### Interactions

Live vaccines should not be given with anakinra as its effect on vaccine efficacy or the risk of infection transmission is unknown.

The risk of serious infection and neutropenia is increased when anakinra and etanercept are used together (see under Infliximab, p.71); a similar effect may occur with other TNF antagonists. The use of anakinra with etanercept or other TNF inhibitors is not recommended.

### Pharmacokinetics

After subcutaneous doses, peak plasma concentrations of anakinra are reached in 3 to 7 hours. Its terminal half-life is about 4 to 6 hours. Anakinra is excreted mainly in the urine.

### Uses and Administration

Anakinra is a recombinant receptor antagonist of interleukin-1 (p.2325), an inflammatory mediator found in the plasma and synovial fluid of patients with rheumatoid arthritis.

Anakinra is used for the treatment of the signs and symptoms of moderate to severely active rheumatoid arthritis in patients who have had an inadequate response to methotrexate or another disease-modifying antirheumatic drug (DMARD) alone (but see below). In the UK, it is only licensed for use with methotrexate; however, in the USA, it may be given either alone or with another DMARD, although not one that inhibits TNF (see Interactions, above). The usual dose in adults is 100 mg once daily by subcutaneous injection. The dose should be given at about the same time each day.

Anakinra has been tried in septic shock and graft-versus-host disease in transplant recipients, but results were disappointing.

**Administration in renal impairment.** Caution may be advisable if anakinra is used in patients with renal impairment. A study[1] in patients with varying degrees of renal function indicated that no dosage adjustment was needed for anakinra in patients with mild or moderate renal impairment but dosage on alternate days appeared advisable in those with severe renal impairment. US licensed product information also recommends alternate-day dosing in patients with severe impairment or end-stage disease (creatinine clearance less than 30 mL/minute). However, in the UK, licensed product information contra-indicates use in those with this degree of impairment.

Dialysis does not affect anakinra concentrations to any significant degree.

1. Yang B-B, *et al.* Pharmacokinetics of anakinra in subjects with different levels of renal function. *Clin Pharmacol Ther* 2003; **74:** 85–94.

**Familial Mediterranean fever.** For mention of anakinra having been tried in familial Mediterranean fever, see p.557.

**Rheumatoid arthritis.** In the UK, anakinra is licensed for the treatment of rheumatoid arthritis (p.11) in patients with an inadequate response to methotrexate alone; however, NICE does not recommend its use except in the context of a controlled, long-term clinical study.

References.

1. Bresnihan B, *et al.* Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum* 1998; **41:** 2196–2204.
2. Cohen S, *et al.* Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; **46:** 614–24.
3. Nuki G, *et al.* Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; **46:** 2838–46.
4. Fleischmann RM, *et al.* Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: a large, international, multicenter, placebo-controlled trial. *Arthritis Rheum* 2003; **48:** 927–34.
5. NICE. Anakinra for rheumatoid arthritis: Technology Appraisal Guidance 72 (issued November 2003). Available at: http://www.nice.org.uk/nicemedia/pdf/TA072guidance.pdf (accessed 22/06/07)
6. Schiff MH. Durability and rapidity of response to anakinra in patients with rheumatoid arthritis. *Drugs* 2004; **64:** 2493–2501.
7. Waugh J, Perry CM. Anakinra: a review of its use in the management of rheumatoid arthritis. *BioDrugs* 2005; **19:** 189–202.
8. Reiff A. The use of anakinra in juvenile arthritis. *Curr Rheumatol Rep* 2005; **7:** 434–40.
9. den Broeder AA, *et al.* Observational study on efficacy, safety, and drug survival of anakinra in rheumatoid arthritis patients in clinical practice. *Ann Rheum Dis* 2006; **65:** 760–2.
10. Burger D, *et al.* Is IL-1 a good therapeutic target in the treatment of arthritis? *Best Pract Res Clin Rheumatol* 2006; **20:** 879–96.

### Preparations

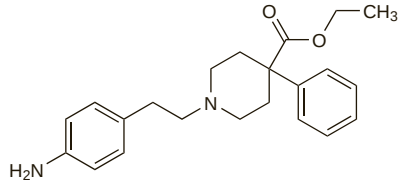
**Proprietary Preparations** (details are given in Part 3)
***Austral.:*** Kineret; ***Canad.:*** Kineret; ***Cz.:*** Kineret; ***Denm.:*** Kineret; ***Fin.:*** Kineret; ***Fr.:*** Kineret; ***Ger.:*** Kineret; ***Gr.:*** Kineret; ***Irl.:*** Kineret; ***Ital.:*** Kineret; ***Neth.:*** Kineret; ***Norw.:*** Kineret; ***Pol.:*** Kineret; ***Port.:*** Kineret; ***Spain:*** Kineret; ***Swed.:*** Kineret; ***UK:*** Kineret; ***USA:*** Kineret.

## Anileridine *(BAN, rINN)*

Anileridiini; Anileridin; Anileridina; Anilé ridine; Anileridinum. Ethyl 1-(4-aminophenethyl)-4-phenylpiperidine-4-carboxylate.

Анилеридин

$C_{22}H_{28}N_2O_2$ = 352.5.
*CAS — 144-14-9.*
*ATC — N01AH05.*
*ATC Vet — QN01AH05.*



**Pharmacopoeias.** In *US.*
**USP 31** (Anileridine). A white to yellowish-white, odourless or practically odourless, crystalline powder. When exposed to light and air it oxidises and darkens in colour. It exhibits polymorphism, and of two crystalline forms observed, one melts at about 80° and the other at about 89°. Very slightly soluble in water; soluble 1 in 2 of alcohol and 1 in 1 of chloroform; soluble in ether but solutions may be turbid. Store in airtight containers. Protect from light.

## Anileridine Hydrochloride *(BANM, rINNM)*

Anilé ridine, Chlorhydrate d'; Anileridini Hydrochloridum; Hidrocloruro de anileridina.

Анилеридина Гидрохлорид

$C_{22}H_{28}N_2O_2$,2HCl = 425.4.
*CAS — 126-12-5.*

**Pharmacopoeias.** In *US.*
**USP 31** (Anileridine Hydrochloride). A white or nearly white odourless crystalline powder. Soluble 1 in 5 of water and 1 in 80 of alcohol; practically insoluble in chloroform and in ether. pH of a 5% solution in water is 2.5 to 3.0. Store in airtight containers. Protect from light.

## Anileridine Phosphate *(BANM, rINNM)*

Anilé ridine, Phosphate d'; Anileridini Phosphas; Fosfato de anileridina.

Анилеридина Фосфат

$C_{22}H_{28}N_2O_2$,$H_3PO_4$ = 450.5.
*CAS — 4268-37-5.*

### Profile

Anileridine, a phenylpiperidine derivative, is an opioid analgesic (p.101) chemically related to pethidine (p.113) and with similar actions. It has been used as the hydrochloride in the management of moderate to severe pain. Anileridine has also been given by injection as the phosphate.

### Preparations

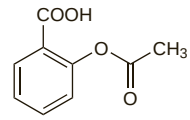
***USP 31:*** Anileridine Hydrochloride Tablets; Anileridine Injection.

## Aspirin *(BAN)*

Acetilsalicílico, ácido; Acetilsalicilo rūgštis; Acetilszalicilsav; Acetylsal. Acid; Acetylsalicylic Acid; Acetylsalicylsyra; Acide acétylsalicylique; Acidum acetylsalicylicum; Asetilsalisilik Asit; Asetyylisalisyylihappo; Kwas acetylosalicylowy; Kyselina acetylsalicylová; Polopiryna; Salicylic Acid Acetate. *O*-Acetylsalicylic acid; 2-Acetoxybenzoic acid.

Аспирин

$C_9H_8O_4$ = 180.2.
*CAS — 50-78-2.*
*ATC — A01AD05; B01AC06; N02BA01.*
*ATC Vet — QA01AD05; QB01AC06; QN02BA01.*



NOTE. The use of the name Aspirin is limited; in some countries it is a trade-mark.
Compounded preparations of aspirin may be represented by the following names:

- Co-codaprin (*BAN*)—aspirin 50 parts and codeine phosphate 1 part (w/w)
- Co-codaprin (*PEN*)—aspirin and codeine phosphate.

**Pharmacopoeias.** In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*
**Ph. Eur. 6.2** (Acetylsalicylic Acid; Aspirin BP 2008). White or almost white, crystalline powder or colourless crystals. Slightly soluble in water; freely soluble in alcohol. Store in airtight containers.
**USP 31** (Aspirin). White crystals, commonly tubular or needle-like, or white crystalline powder; odourless or has a faint odour. Is stable in dry air; in moist air it gradually hydrolyses to salicylic and acetic acids. Soluble 1 in 300 of water, 1 in 5 of alcohol, 1 in 17 of chloroform, and 1 in 10 to 15 of ether; sparingly soluble in absolute ether. Store in airtight containers.

### Adverse Effects and Treatment

Aspirin has many properties in common with the non-aspirin NSAIDs, the adverse effects of which are described on p.96.

The most common adverse effects of therapeutic doses of aspirin are gastrointestinal disturbances such as nausea, dyspepsia, and vomiting. Gastrointestinal symptoms may be minimised by giving aspirin with food. Irritation of the gastric mucosa with erosion, ulceration, haematemesis, and melaena may occur. Histamine $H_2$-antagonists, proton pump inhibitors, and prostaglandin analogues such as misoprostol may be used in the management of NSAID-induced ulceration (see Peptic Ulcer Disease, p.1702), including that caused by aspirin. Slight blood loss, which is often asymptomatic, may occur in about 70% of patients; it is not usually of clinical significance but may, in a few patients, cause iron-deficiency anaemia during long-term therapy. Such occult blood loss is not affected by giving aspirin with food but may be reduced by use of enteric-coated or other modified-release tablets, $H_2$-antagonists, or high doses of antacids. Major upper gastrointestinal bleeding occurs rarely.

Some persons, especially those with asthma, chronic urticaria, or chronic rhinitis, exhibit notable hypersensitivity to aspirin (see also below), which may provoke reactions including urticaria and other skin eruptions, angioedema, rhinitis, and severe, even fatal, paroxysmal bronchospasm and dyspnoea. Persons sensitive to aspirin often exhibit cross-sensitivity to other NSAIDs.

Aspirin increases bleeding time, decreases platelet adhesiveness, and, in large doses, can cause hypoprothrombinaemia. It may cause other blood disorders, including thrombocytopenia.

Aspirin and other salicylates may cause hepatotoxicity, particularly in patients with juvenile idiopathic arthritis or other connective tissue disorders. In children the use of aspirin has been implicated in some cases of Reye's syndrome, leading to severe restrictions on the indications for aspirin therapy in children. For further details see under Reye's Syndrome, below.

Aspirin given rectally may cause local irritation; anorectal stenosis has been reported.

Mild chronic salicylate intoxication, or salicylism, usually occurs only after repeated use of large doses. Salicylism can also occur following excessive topical application of salicylates. Symptoms include dizziness, tinnitus, deafness, sweating, nausea and vomiting, headache, and confusion, and may be controlled by reducing the dosage. Tinnitus can occur at the plasma concentrations of 150 to 300 micrograms/mL required for optimal anti-inflammatory activity; more serious adverse effects occur at concentrations above 300 micrograms/mL. Symptoms of more severe intoxication or of acute poisoning following overdosage include hyperventilation, fever, restlessness, ketosis, and respiratory alkalosis and metabolic acidosis. Depression of the CNS may lead to coma; cardiovascular collapse and respiratory failure may also occur. In children drowsiness and metabolic acidosis commonly occur; hypoglycaemia may be severe.

In acute oral salicylate overdosage the UK National Poisons Information Service recommends that repeated oral doses of activated charcoal be given if the patient is suspected of ingesting more than 125 mg/kg of salicylate within 1 hour of presentation. Activated charcoal not only prevents the absorption of any salicylate remaining in the stomach but also aids the elimination of any that has been absorbed.

Measurement of plasma-salicylate concentration should be carried out in patients who have ingested more than 125 mg/kg of salicylate, although the severity of poisoning cannot be estimated from plasma concentrations alone. Absorption of aspirin can be delayed by reduced gastric emptying, formation of concretions in the stomach, or as a result of ingestion of enteric-coated preparations. In consequence, plasma concentrations should be measured at least 2 hours (symptomatic patients) or 4 hours (asymptomatic patients) after ingestion and repeated 2 hours later. Patients who overdose with enteric preparations require continual monitoring of plasma concentrations.

Fluid and electrolyte management is essential to correct acidosis, hyperpyrexia, hypokalaemia, and dehydration. Intravenous sodium bicarbonate is given to enhance urinary salicylate excretion if plasma salicylate concentrations exceed 500 micrograms/mL (350 micrograms/mL in children under 5 years). Haemodialysis or haemoperfusion are also effective methods of removing salicylate from the plasma. The *BNF* considers haemodialysis the method of choice in severe poisoning; it should be seriously considered when the plasma salicylate concentration is more than 700 micrograms/mL or if there is severe metabolic acidosis. Vulnerable patients such as children or the elderly may require dialysis at an earlier stage.

◊ References to salicylate toxicity and its management.


1. Notarianni L. A reassessment of the treatment of salicylate poisoning. *Drug Safety* 1992; **7:** 292–303.
2. Woods D, *et al.* Acute toxicity of drugs: salicylates. *Pharm J* 1993; **250:** 576–8.
3. Collee GG, Hanson GC. The management of acute poisoning. *Br J Anaesth* 1993; **70:** 562–73.
4. Watson JE, Tagupa ET. Suicide attempt by means of aspirin enema. *Ann Pharmacother* 1994; **28:** 467–9.
5. Dargan PI, *et al.* An evidence based flowchart to guide the management of acute salicylate (aspirin) overdose. *Emerg Med J* 2002; **19:** 206–9.
6. Rivera W, *et al.* Delayed salicylate toxicity at 35 hours without early manifestations following a single salicylate ingestion. *Ann Pharmacother* 2004; **38:** 1186–8. Correction. *ibid.* 2006; **40:** 999.


**Effects on the blood.** Although it has beneficial effects on platelets, aspirin can cause adverse blood effects. An indication of this toxicity is given by an early reference[1] to reports submitted to the UK CSM. There were 787 reports of adverse reactions to aspirin reported to the CSM between June 1964 and January 1973. These included 95 reports of blood disorders (17 fatal) including thrombocytopenia (26; 2 fatal), aplastic anaemia (13; 7 fatal), and agranulocytosis or pancytopenia (10; 2 fatal). Aspirin has also been associated with haemolytic anaemia in patients with G6PD deficiency.[2]


1. Cuthbert MF. Adverse reactions to non-steroidal antirheumatic drugs. *Curr Med Res Opin* 1974; **2:** 600–9.
2. Magee P, Beeley L. Drug-induced blood dyscrasias. *Pharm J* 1991; **246:** 396–7.


**Effects on the cardiovascular system.** Salicylate poisoning may result in cardiovascular collapse but details of such cases have not been widely reported. In 2 patients with salicylate intoxication asystole developed after intravenous diazepam.[1] It was suggested that diazepam-induced respiratory depression affected the acid–base balance so that the concentration of non-ionised membrane-penetrating fraction of salicylate was increased. Fatal aspirin intoxication in a 5-year-old child was marked by hypotension and rapidly progressive cardiac symptoms including ventricular tachycardia and AV block.[2] Extensive myocardial necrosis was found at autopsy.

For reference to the effects of aspirin on blood pressure compared with other NSAIDs, see p.96.


1. Berk WA, Andersen JC. Salicylate-associated asystole: report of two cases. *Am J Med* 1989; **86:** 505–6.
2. Peña-Alonso YR, *et al.* Aspirin intoxication in a child associated with myocardial necrosis: is this a drug-related lesion? *Pediatr Dev Pathol* 2003; **6:** 342–7.


**Effects on the gastrointestinal tract.** Clinical and epidemiological evidence suggests that aspirin produces dose-related gastrointestinal toxicity[1,2] that is sometimes, but rarely, fatal.[2] Meta-analysis[3] suggests that the risk of gastrointestinal bleeding is not significantly lowered with the use of oral low-dose aspirin (less than 300 mg daily). A systematic review[4] of observational epidemiologic studies also concurred with this finding. More recently, a systematic review[5] of randomised, controlled studies found that although low-dose aspirin (up to 325 mg daily) increased the risk of major bleeding including gastrointestinal bleeding by twofold when compared to placebo, the actual risk of bleeding was modest; for every 833 patients taking low-dose aspirin for cardiovascular prophylaxis only 1 additional major bleeding episode will occur annually. In another, population-based study,[6] the annual excess risk of upper gastrointestinal complications was about an extra 5 cases per 1000 patients; however, the excess risk varied with underlying gastrointestinal risk factors such as old age and might exceed an extra 10 cases per 1000 patients in a higher risk group comprising over 10% of aspirin users. It has been suggested that very small doses of aspirin can produce prophylactic benefits in cardiovascular disease without the risk of gastrointestinal toxicity,[7] although others have reported gastric injury even with doses of 10 mg daily.[8]

There appears to be no convincing evidence that the risk of major gastrointestinal bleeding associated with a 75-mg dose is reduced by using enteric-coated or modified-release formulations rather than soluble aspirin,[3,4,9] although individual studies have reported a reduction in acute mucosal injury with enteric coating.[10] All known NSAIDs have the potential for causing acute damage to the gastric mucosa (see p.97), and comparative studies of acute gastric mucosal damage caused by such drugs consistently associate aspirin with the most severe lesions.[1] Gastric mucosal injury can occur even with cutaneous application.[11]


1. Graham DY, Smith JL. Aspirin and the stomach. *Ann Intern Med* 1986; **104:** 390–8.
2. Roderick PJ, *et al.* The gastrointestinal toxicity of aspirin: an overview of randomised controlled trials. *Br J Clin Pharmacol* 1993; **35:** 219–26.
3. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. *BMJ* 2000; **321:** 1183–7.
4. Garcia Rodríguez LA, *et al.* Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies. *Br J Clin Pharmacol* 2001; **52:** 563–71.
5. McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *Am J Med* 2006; **119:** 624–38.
6. Hernández-Díaz S, García Rodríguez LA. Cardioprotective aspirin users and their excess risk of upper gastrointestinal complications. *BMC Med* 2006; **4:** 22. Available at: http://www.biomedcentral.com/content/pdf/1741-7015-4-22.pdf (accessed 11/12/06)
7. Lee M, *et al.* Dose effects of aspirin on gastric prostaglandins and stomach mucosal injury. *Ann Intern Med* 1994; **120:** 184–9.
8. Cryer B, Feldman M. Effects of very low dose daily, long-term aspirin therapy on gastric, duodenal, and rectal prostaglandin levels and on mucosal injury in healthy humans. *Gastroenterology* 1999; **117:** 17–25.
9. Anonymous. Which prophylactic aspirin? *Drug Ther Bull* 1997; **35:** 7–8.
10. Cole AT, *et al.* Protection of human gastric mucosa against aspirin—enteric coating or dose reduction? *Aliment Pharmacol Ther* 1999; **13:** 187–93.
11. Cryer B, *et al.* Effects of cutaneous aspirin on the human stomach and duodenum. *Proc Assoc Am Physicians* 1999; **111:** 448–56.


**Effects on hearing.** Studies have shown that tinnitus develops at serum-salicylate concentrations above 200 micrograms/mL.[1] However, there appears to be considerable intersubject variation in the response of the ear to salicylate;[2] tinnitus may occur at lower concentrations, whereas patients with pre-existing hearing loss may not experience tinnitus despite serum-salicylate concentrations of 311 to 677 micrograms/mL.[1] A graded increase in intensity of ototoxicity with increasing salicylate dose and plasma concentration has been demonstrated.[2] For example, at an average total plasma-salicylate concentration of 110 micrograms/mL, the hearing loss at any given frequency was about 12 decibels; such a deficit might be relevant to patients with pre-existing hearing impairment.[2]


1. Mongan E, *et al.* Tinnitus as an indication of therapeutic serum salicylate levels. *JAMA* 1973; **226:** 142–5.
2. Day RO, *et al.* Concentration-response relationships for salicylate-induced ototoxicity in normal volunteers. *Br J Clin Pharmacol* 1989; **28:** 695–702.


**Effects on the kidneys.** Although abuse of combined analgesic preparations containing aspirin has been implicated in the development of analgesic nephropathy, kidney damage associated with the therapeutic use of aspirin alone appears to be comparatively rare. Many studies have failed to find an increased risk of renal damage in patients taking aspirin.[1-9]


1. New Zealand Rheumatism Association Study. Aspirin and the kidney. *BMJ* 1974; **1:** 593–6.
2. Walker BR, *et al.* Aspirin and renal function. *N Engl J Med* 1977; **297:** 1405.
3. Akyol SM, *et al.* Renal function after prolonged consumption of aspirin. *BMJ* 1982; **284:** 631–2.
4. Bonney SL, *et al.* Renal safety of two analgesics used over the counter: ibuprofen and aspirin. *Clin Pharmacol Ther* 1986; **40:** 373–7.
5. Sandler DP, *et al.* Analgesic use and chronic renal disease. *N Engl J Med* 1989; **320:** 1238–43.
6. Pommer W, *et al.* Regular analgesic intake and the risk of end-stage renal failure. *Am J Nephrol* 1989; **9:** 403–12.
7. Dubach UC, *et al.* An epidemiologic study of abuse of analgesic drugs: effects of phenacetin and salicylate on mortality and cardiovascular morbidity (1968 to 1987). *N Engl J Med* 1991; **324:** 155–60.
8. Perneger TV, *et al.* Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. *N Engl J Med* 1994; **331:** 1675–9.
9. Rexrode K, *et al.* Analgesic use and renal function in men. *JAMA* 2001; **286:** 315–21.


**Effects on the liver.** Aspirin-induced hepatic injury is generally mild and manifests as a mild to moderate elevation in aminotransferase values; however, there is a risk of severe liver injury.[1] One review[2] reported an increase in aminotransferase values in 59 of 439 patients given aspirin; the increase was considered to be probably related to aspirin in 23. Hepatotoxicity appears to be correlated with serum-salicylate concentrations greater than 150 micrograms/mL and with active rheumatoid disease. Aspirin-induced liver injury is usually reversible on stopping the drug.[2]

See also under Reye's Syndrome, below.


1. Lewis JH. Hepatic toxicity of nonsteroidal anti-inflammatory drugs. *Clin Pharm* 1984; **3:** 128–38.
2. Freeland GR, *et al.* Hepatic safety of two analgesics used over the counter: ibuprofen and aspirin. *Clin Pharmacol Ther* 1988; **43:** 473–9.


**Effects on the mouth.** Aspirin burn (ulceration of the mucosal layer of the lips) developed in a 26-year-old woman after taking an aspirin-containing powder for a migraine.[1] The woman had swallowed the powder undissolved rather than adding to water.


1. Dellinger TM, Livingston HM. Aspirin burn of the oral cavity. *Ann Pharmacother* 1998; **32:** 1107.


**Hypersensitivity.** The main clinical features of patients who have aspirin hypersensitivity include middle-age, female sex, diagnoses of asthma or rhinitis, a personal or family history of atopy, and a history of nasal polyps.[1,2] Aspirin sensitivity occurring with asthma and nasal polyps has been referred to in some reports as the 'aspirin triad'. Other sensitivities often found concomitantly include allergy to food dyes such as tartrazine and to drugs such as other NSAIDs.

The prevalence of aspirin-induced asthma can vary according to the method used to measure it. A systematic review[3] calculated the prevalence of aspirin-induced asthma to be 21% in the general adult asthma population and 5% in children when determined by oral provocation testing. However, when based on medical history alone it was only 2.7% in adults and 2% in children. In another study[4] using data from patient questionnaires the prevalence of aspirin-induced asthma was 10 to 11% in patients with asthma and 2.5% in non-asthmatics.

There is considerable cross-reactivity between aspirin and other NSAIDs and it is generally recommended that patients who have had a hypersensitivity reaction to aspirin or any other NSAID should avoid all NSAIDs. In a systematic review[3] cross-sensitivity to other NSAIDs (ibuprofen, diclofenac, and naproxen) occurred in over 90% of those patients with aspirin-induced asthma. Paracetamol is usually safe in patients sensitive to aspirin and cross-sensitivity to paracetamol has been calculated as about 7%.[3] Based on these figures, it is considered that less than 2% of asthmatic patients would be likely to react to both paracetamol and aspirin.

The response to individual NSAIDs is believed to be closely linked to the extent to which they inhibit prostaglandin synthesis.[5,6] There may be a dose threshold below which no detectable symptoms occur and patients who may be tolerant of regular low-dose aspirin can develop symptoms when they take larger doses.[6] Some[6] use a formal challenge with a 300-mg oral dose of aspirin to confirm a diagnosis of NSAID sensitivity but others[7] consider this to be a dangerous technique and use inhalation of lysine aspirin which they consider to be a safer and more predictable alternative. Intranasal challenge with lysine aspirin has also been used.[8,9]


1. Kwoh CK, Feinstein AR. Rates of sensitivity reactions to aspirin: problems in interpreting the data. *Clin Pharmacol Ther* 1986; **40:** 494–505.
2. Schiavino D, *et al.* The aspirin disease. *Thorax* 2000; **55** (suppl 2): S66–S69.
3. Jenkins C, *et al.* Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. *BMJ* 2004; **328:** 434–7.
4. Vally H, *et al.* The prevalence of aspirin intolerant asthma (AIA) in Australian asthmatic patients. *Thorax* 2002; **57:** 569–74.

5. Power I. Aspirin-induced asthma. *Br J Anaesth* 1993; **71:** 619–21.
6. Frew A. Selected side-effects: 13. non-steroidal anti-inflammatory drugs and asthma. *Prescribers' J* 1994; **34:** 74–7.
7. Davies BH. NSAIDs and asthma. *Prescribers' J* 1994; **34:** 163–4.
8. Casadevall J *et al*. Intranasal challenge with aspirin in the diagnosis of aspirin intolerant asthma: evaluation of nasal response by acoustic rhinometry. *Thorax* 2000; **55:** 921–4.
9. Alonso-Llamazares A, *et al*. Nasal provocation test (NPT) with aspirin: a sensitive and safe method to diagnose aspirin-induced asthma (AIA). *Allergy* 2002; **57:** 632–5.

***DESENSITISATION.*** Successful desensitisation has been achieved using oral aspirin challenge protocols.[1-5] Incremental doses of aspirin (traditionally starting at 30 mg) are given until an allergic response occurs; aspirin is readministered at the dose that caused the response and again incremental doses are given until finally a 650-mg dose is tolerated.[1,2] After desensitisation, an interruption of continuous aspirin dosage results in the reappearance of sensitivity.

1. Asad SI, *et al*. Effect of aspirin in "aspirin sensitive" patients. *BMJ* 1984; **288:** 745–8.
2. Stevenson DD. Desensitization of aspirin-sensitive asthmatics: a therapeutic alternative? *J Asthma* 1983; **20:** 31–8.
3. Gollapudi RR, *et al*. Aspirin sensitivity: implications for patients with coronary artery disease. *JAMA* 2004; **292:** 3017–23.
4. Cormican LJ, *et al*. Improvements in an oral aspirin challenge protocol for the diagnosis of aspirin hypersensitivity. *Clin Exp Allergy* 2005; **35:** 717–22.
5. Pfaar O, Klimek L. Aspirin desensitization in aspirin intolerance: update on current standards and recent improvements. *Curr Opin Allergy Clin Immunol* 2006; **6:** 161–6.

**Hypoglycaemia.** A review of the literature[1] on drug-induced hypoglycaemia highlighted the fact that overdosage with salicylates could produce hypoglycaemia in children. Although therapeutic doses of salicylates in adults can lower blood-glucose concentrations in diabetic and non-diabetic subjects alike, opinion on the clinical significance of this effect varies. Salicylates have been implicated in a few cases of hypoglycaemia in adults[1] and some[2] suggest that patients with renal impairment or those receiving large doses, such as in the treatment of rheumatoid arthritis, may be at risk. Hypoglycaemia has been reported in a patient with renal failure after excessive application of a topical preparation containing salicylic acid.[3]

1. Seltzer HS. Drug-induced hypoglycemia: a review of 1418 cases. *Endocrinol Metab Clin North Am* 1989; **18:** 163–83.
2. Pandit MK, *et al*. Drug-induced disorders of glucose tolerance. *Ann Intern Med* 1993; **118:** 529–39.
3. Raschke R, *et al*. Refractory hypoglycemia secondary to topical salicylate intoxication. *Arch Intern Med* 1991; **151:** 591–3.

**Reye's syndrome.** Reye's syndrome is a disorder characterised by acute encephalopathy and fatty degeneration of the liver. It occurs almost exclusively in young children although cases have been seen[1] in patients over the age of 12. Many factors may be involved in its aetiology but it typically occurs after a viral infection such as chickenpox or influenza and may be precipitated by a chemical trigger. Several large studies, as well as individual case reports, have found a link between Reye's syndrome and the prior ingestion of aspirin.[2-6] The evidence for other salicylates could not be adequately evaluated.[4] Although the role of aspirin and possibly other salicylates in the pathogenesis of Reye's syndrome remains to be determined, the use of aspirin and other acetylated salicylates as analgesics or antipyretics is generally considered contra-indicated in children under the age of 12 years and, in some countries, in teenagers. For example, the UK CSM has recommended that all children under 16 should not take aspirin.[7] (This advice superseded their earlier recommendations to avoid aspirin during fever or viral infection in children under 16 years; the Committee felt that this advice was too complex for products on general sale and, given the wide availability of other analgesic preparations, there was no need to expose this age group to any risk.) Some countries also extend these recommendations to non-acetylated salicylates. One group of workers[8] who re-examined some of the original studies suggested that there might also be a link between Reye's syndrome and the use of antiemetics, phenothiazines, and some other antihistamines, but their conclusions have been criticised.[9] More recently, others[10] have suggested that Reye's syndrome was caused by a viral mutation or the result of misdiagnoses of metabolic disorders but again these conclusions have been questioned.[6,11]

1. Hall SM, Lynn R. Reye's syndrome. *N Engl J Med* 1999; **341:** 845–6.
2. Waldman RJ, *et al*. Aspirin as a risk factor in Reye's syndrome. *JAMA* 1982; **247:** 3089–94.
3. Halpin TJ, *et al*. Reye's syndrome and medication use. *JAMA* 1982; **248:** 687–91.
4. Hurwitz ES, *et al*. Public health service study of Reye's syndrome and medications: report of the main study. *JAMA* 1987; **257:** 1905–11.
5. Hall SM, *et al*. Preadmission antipyretics in Reye's syndrome. *Arch Dis Child* 1988; **63:** 857–66.
6. Glasgow JFT. Reye's syndrome: the case for a causal link with aspirin. *Drug Safety* 2006; **29:** 1111–21.
7. MHRA. Aspirin and Reye's syndrome: questions and answers (issued 4th April, 2003). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019512&RevisionSelectionMethod=LatestReleased (accessed 29/11/06)
8. Casteels-Van Daele M, Eggermont E. Reye's syndrome. *BMJ* 1994; **308:** 919–20.
9. Hall SM. Reye's syndrome. *BMJ* 1994; **309:** 411.
10. Orlowski JP, *et al*. Is aspirin a cause of Reye's syndrome? A case against. *Drug Safety* 2002; **25:** 225–31.
11. Waller P, Suvarna R. Is aspirin a cause of Reye's syndrome? *Drug Safety* 2004; **27:** 71–3.

## Precautions

Aspirin has many properties in common with the non-aspirin NSAIDs, the precautions of which are described on p.98.

Aspirin should be used cautiously, if at all, in patients prone to dyspepsia or known to have a lesion of the gastric mucosa. It should not be given to patients with haemophilia or other haemorrhagic disorders, nor to treat patients with gout (since low doses increase urate concentrations).

Aspirin should be used with caution in patients with asthma or allergic disorders. It should not be given to patients with a history of sensitivity reactions to aspirin or other NSAIDs, including those in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by such drugs (for further details of risk factors see Hypersensitivity under Adverse Effects, above).

Caution is necessary when renal or hepatic function is impaired; aspirin should be avoided in severe renal or hepatic impairment. Aspirin should be used cautiously in dehydrated patients and in the presence of uncontrolled hypertension.

High doses may precipitate acute haemolytic anaemia in patients with G6PD deficiency. Aspirin may interfere with insulin and glucagon control in diabetics (see Hypoglycaemia under Adverse Effects, above).

The use of aspirin in children is extremely limited because of the risk of Reye's syndrome (see under Adverse Effects, above, and under Uses and Administration, below).

Although low-dose aspirin might be used in some pregnant patients, analgesic doses of aspirin should not be used at term as they may be associated with delayed onset and prolongation of labour and with maternal and neonatal bleeding. High doses may cause closure of fetal ductus arteriosus *in utero* and possibly persistent pulmonary hypertension in the newborn (but see Pregnancy, below); kernicterus may occur in jaundiced neonates.

Continuous prolonged use of aspirin should be avoided in the elderly because of the risk of gastrointestinal bleeding.

Aspirin should be stopped several days before scheduled surgical procedures (see below).

Aspirin and other salicylates can interfere with thyroid function tests.

**Breast feeding.** The American Academy of Pediatrics[1] considers that salicylates should be given with caution to breast-feeding mothers, since aspirin has been associated with metabolic acidosis in the infant.[2] The *BNF* also recommends that aspirin should be avoided in breast-feeding mothers because of the possible risk of Reye's syndrome in nursing infants; they also advise that infants with neonatal vitamin K deficiency may be at risk of hypoprothrombinaemia after the regular use of high doses of aspirin in breast-feeding mothers. However, a prospective study[3] found no adverse effects in 15 breast-fed infants whose mothers were receiving aspirin.

1. 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 23/11/06)
2. Clark JH, Wilson WG. A 16-day-old breast-fed infant with metabolic acidosis caused by salicylate. *Clin Pediatr (Phila)* 1981; **20:** 53–4.
3. Ito S, *et al*. Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal medication. *Am J Obstet Gynecol* 1993; **168:** 1393–9.

**Pregnancy.** The potential adverse effects of aspirin when used during pregnancy have been reviewed.[1] Salicylates readily cross the placenta and have been shown to be teratogenic in *animals*. Although some studies and anecdotal reports have implicated aspirin in the formation of congenital abnormalities, most large studies[2-4] have failed to find any significant risk or evidence of teratogenicity. Analysis of data collected by the Slone Epidemiology Unit Birth Defects Study suggests that use of aspirin during the early months of pregnancy, when the fetal heart is developing, is not associated with an increased risk of cardiac defects.[5] The ability of aspirin, however, to alter platelet function may be a potential risk. There have been a few reports of haemorrhagic disorders in infants whose mothers had consumed aspirin during pregnancy[6] and of salicylate-associated haemorrhagic complications in mothers.[7] However, no clinically significant adverse effects on maternal or neonatal bleeding or on fetal ductus flow were reported in a meta-analysis[8] of 6 controlled studies which evaluated low-dose aspirin (less than 325 mg daily) in pregnancy-induced hypertension. Two more recent placebo-controlled studies[9,10] have also observed no clinically significant adverse effects on neonatal bleeding with low-dose aspirin. It appeared that the degree of cyclo-oxygenase inhibition produced by aspirin was unlikely to be great enough to cause premature closure of the ductus arteriosus or to affect the pulmonary blood vessels.[1] See also under Surgical Procedures, below. However, in some studies in patients considered to have high-risk pregnancies the risk of abruptio placentae[11] or consequent perinatal death[12] was increased by maternal dosage with aspirin. For reference to a possible association between aspirin and other NSAIDs and persistent pulmonary hypertension of the newborn, see under NSAIDs, p.99.

Although aspirin has the potential to inhibit uterine contractions of labour it was considered that intermittent or low-dose aspirin was unlikely to inhibit cyclo-oxygenase for long enough to prolong pregnancy or labour.[1]

1. de Swiet M, Fryers G. The use of aspirin in pregnancy. *J Obstet Gynaecol* 1990; **10:** 467–82.
2. Slone D, *et al*. Aspirin and congenital malformations. *Lancet* 1976; **1:** 1373–5.
3. Shapiro S, *et al*. Perinatal mortality and birth-weight in relation to aspirin taken during pregnancy. *Lancet* 1976; **i:** 1375–6.
4. Winship KA, *et al*. Maternal drug histories and central nervous system anomalies. *Arch Dis Child* 1984; **59:** 1052–60.
5. Werler MM, *et al*. The relation of aspirin use during the first trimester of pregnancy to congenital cardiac defects. *N Engl J Med* 1989; **321:** 1639–42.
6. Bleyer WA, Breckenridge RT. Studies on the detection of adverse drug reactions in the newborn II: the effects of prenatal aspirin on newborn hemostasis. *JAMA* 1970; **213:** 2049–53.
7. Collins E, Turner G. Maternal effects of regular salicylate ingestion in pregnancy. *Lancet* 1975; **ii:** 335–7.
8. Imperiale TF, Petrulis AS. A meta-analysis of low-dose aspirin for the prevention of pregnancy-induced hypertensive disease. *JAMA* 1991; **266:** 261–4.
9. Louden KA, *et al*. Neonatal platelet reactivity and serum thromboxane B production in whole blood: the effect of maternal low dose aspirin. *Br J Obstet Gynaecol* 1994; **101:** 203–8.
10. Dasari R, *et al*. Effect of maternal low dose aspirin on neonatal platelet function. *Indian Pediatr* 1998; **35:** 507–11.
11. Sibai BM, *et al*. Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. *N Engl J Med* 1993; **329:** 1213–18.
12. Hamid R, *et al*. Low dose aspirin in women with raised maternal serum alpha-fetoprotein and abnormal Doppler waveform patterns from the uteroplacental circulation. *Br J Obstet Gynaecol* 1994; **101:** 481–4.

**Resistance.** Some patients given aspirin for the management of cardiovascular disease do not respond to treatment, a phenomenon that has been described as aspirin resistance. At present, aspirin resistance is poorly understood and further studies are needed to define it.

References

1. Sanderson S, *et al*. Narrative review: aspirin resistance and its clinical implications. *Ann Intern Med* 2005; **142:** 370–80.
2. Hankey GJ, Eikelboom JW. Aspirin resistance. *Lancet* 2006; **367:** 606–17.
3. Michos ED, *et al*. Aspirin and clopidogrel resistance. *Mayo Clin Proc* 2006; **81:** 518–26.
4. Undas A, *et al*. Antithrombotic properties of aspirin and resistance to aspirin: beyond strictly antiplatelet actions. *Blood* 2007; **109:** 2285–92.
5. Dalen JE. Aspirin resistance: is it real? Is it clinically significant? *Am J Med* 2007; **120:** 1–4.

**Surgical procedures.** Aspirin prolongs bleeding time, mainly by inhibiting platelet aggregation. This effect is irreversible and new platelets must be released into the circulation before bleeding time can return to normal. Therefore aspirin therapy should be stopped several days before surgical procedures. In some clinical situations, aspirin may have been given shortly before a surgical procedure. When emergency coronary bypass surgery is required for myocardial infarction, most patients would have received aspirin as part of the initial treatment for infarction. Perioperative bleeding, transfusion requirements, and surgical re-exploration rates may be increased when aspirin is given.[1] However, some studies[2,3] have shown that the increase in bleeding is not significant; in addition, there have been reports that pre-operative aspirin may reduce the rate of perioperative myocardial infarction (with aprotinin),[4] improve oxygenation,[5] and even decrease mortality.[3,6] Desmopressin may reduce the risk of perioperative bleeding (see under Haemorrhagic Disorders, p.2187).

Aspirin is sometimes given during the second and third trimester for the prevention of pregnancy-induced hypertensive disease (see under Hypertension, p.1171). Studies indicate that when given in a dose of 325 mg daily or less, clinically significant effects on maternal or neonatal bleeding do not occur.[7] Some have suggested that aspirin therapy may increase the risk of formation of extradural haematoma thus making epidural anaesthesia inadvisable[8] but a subsequent study[9] found that low-dose aspirin during pregnancy did not increase the risk of bleeding complications during epidural anaesthesia.

Patients on low-dose aspirin, in whom tourniquets are used for nerve blocks or other procedures, may be at increased risk of developing purpuric rash.[10]

It has been suggested that in patients undergoing dermatological,[11] or minor dental[12] surgery, aspirin need only be stopped before surgery in those patients with a prolonged bleeding time, whereas patients with a normal bleeding time could continue therapy.


1. Goldman S, *et al.* Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy: results of a Veterans Administration Cooperative Study. *Circulation* 1988; **77:** 1324–32.
2. Reich DL, *et al.* Aspirin does not increase homologous blood requirements in elective coronary bypass surgery *Anesth Analg* 1994; **79:** 4–8.
3. Dacey LJ, *et al.* Effect of preoperative aspirin use on mortality in coronary artery bypass grafting patients. *Ann Thorac Surg* 2000; **70:** 1986–90.
4. Klein M, *et al.* Aprotinin counterbalances an increased risk of peri-operative hemorrhage in CABG patients pre-treated with aspirin. *Eur J Cardiothorac Surg* 1998; **14:** 360–6.
5. Gerrah R, *et al.* Preoperative aspirin administration improves oxygenation in patients undergoing coronary artery bypass grafting. *Chest* 2005; **127:** 1622–6.
6. Bybee KA, *et al.* Preoperative aspirin therapy is associated with improved postoperative outcomes in patients undergoing coronary artery bypass grafting. *Circulation* 2005; **112** (suppl I): I286–I292.
7. Imperiale TF, Petrulis AS. A meta-analysis of low-dose aspirin for the prevention of pregnancy-induced hypertensive disease. *JAMA* 1991; **266:** 260–4.
8. Macdonald R. Aspirin and extradural blocks. *Br J Anaesth* 1991; **66:** 1–3.
9. Sibai BM, *et al.* Low-dose aspirin in nulliparous women: safety of continuous epidural block and correlation between bleeding time and maternal-neonatal bleeding complications. *Am J Obstet Gynecol* 1995; **172:** 1553–7.
10. Runcie CJ, *et al.* Aspirin and intravenous regional blocks. *Br J Hosp Med* 1990; **43:** 229–30.
11. Lawrence C, *et al.* Effect of aspirin and nonsteroidal antiinflammatory drug therapy on bleeding complications in dermatologic surgical patients. *J Am Acad Dermatol* 1994; **31:** 988–92.
12. Madan GA, *et al.* Minor oral surgery without stopping daily low-dose aspirin therapy: a study of 51 patients. *J Oral Maxillofac Surg* 2005; **63:** 1262–5.


## Interactions

Aspirin has many properties in common with the non-aspirin NSAIDs, the interactions of which are described on p.99.

Some of the effects of aspirin on the gastrointestinal tract are enhanced by alcohol. Use of gold compounds with aspirin may exacerbate aspirin-induced liver damage.

Use of aspirin with dipyridamole may result in an increase in plasma-salicylate concentrations. Drugs such as metoclopramide in patients with migraine headache result in earlier absorption of aspirin and higher peak plasma-salicylate concentrations. Metoprolol may also increase peak plasma-salicylate concentrations. Salicylate intoxication has occurred in patients on high-dose salicylate regimens and carbonic anhydrase inhibitors.

Plasma-salicylate concentrations may be reduced by corticosteroids. This interaction is likely to be important in patients receiving high-dose long-term salicylate treatment. Conversely, salicylate toxicity may occur if corticosteroids are withdrawn. Also the risk of gastrointestinal bleeding and ulceration associated with aspirin is increased when used with corticosteroids. Antacids may increase the excretion of aspirin in alkaline urine.

Aspirin may increase the activity of coumarin anticoagulants, sulfonylurea hypoglycaemic drugs, zafirlukast, methotrexate, phenytoin, and valproate. Aspirin diminishes the effects of uricosurics such as probenecid and sulfinpyrazone. The manufacturer of mifepristone advises of a theoretical risk that prostaglandin synthetase inhibition by aspirin or NSAIDs may alter the efficacy of mifepristone.

Use of aspirin with other NSAIDs should be avoided because of the increased risk of adverse effects; the cardioprotective effects of aspirin may be abolished by ibuprofen and possibly other NSAIDS. Aspirin may decrease the plasma concentration of some other NSAIDs, for example, fenbufen, indometacin, and piroxicam.


◊ References.

1. Miners JO. Drug interactions involving aspirin (acetylsalicylic acid) and salicylic acid. *Clin Pharmacokinet* 1989; **17:** 327–44.
2. Abebe W. Herbal medication: potential for adverse interactions with analgesic drugs. *J Clin Pharm Ther* 2002; **27:** 391–401.
3. Gaziano JM, Gibson CM. Potential for drug-drug interactions in patients taking analgesics for mild-to-moderate pain and low-dose aspirin for cardioprotection. *Am J Cardiol* 2006; **97:** 23–9.


**ACE inhibitors.** For a discussion of aspirin and other NSAIDs reducing the activity of ACE inhibitors, see p.1197.

**Antiepileptics.** Aspirin may inhibit the metabolism of *valproate*; for further details, see Analgesics, p.510.

**Antifungals.** Plasma-salicylate concentrations in an 8-year-old child receiving long-term aspirin therapy for rheumatic heart disease were markedly reduced when treatment with *griseofulvin* was started.[1] It was suggested that griseofulvin might interfere with absorption of aspirin.


1. Phillips KR, *et al.* Griseofulvin significantly decreases serum salicylate concentrations. *Pediatr Infect Dis J* 1993; **12:** 350–2.


**Calcium-channel blockers.** The antiplatelet effects of aspirin and calcium-channel blockers may be increased when they are used together; there have been isolated reports[1,2] of disturbed haemostasis including abnormal bruising, prolonged bleeding times and ecchymosis in patients taking aspirin and *verapamil* concurrently.


1. Ring ME, *et al.* Clinically significant antiplatelet effects of calcium-channel blockers. *J Clin Pharmacol* 1986; **26:** 719–20.
2. Verzino E, *et al.* Verapamil-aspirin interaction. *Ann Pharmacother* 1994; **28:** 536–7.


**General anaesthetics.** For the effect of aspirin on *thiopental* anaesthesia, see p.1796.

**NSAIDs.** It has been suggested that *ibuprofen* and possibly other *NSAIDs* may reduce the cardioprotective effect of aspirin. A study[1] involving 7107 patients found that cardiovascular mortality was increased in patients taking low-dose aspirin for cardiovascular disease when also taking ibuprofen (adjusted hazard ratio 1.73 times that of patients not taking ibuprofen). Another study[2] found that although taking low-dose aspirin or NSAIDs alone decreased the incidence of myocardial infarction, there was a non-significant increase in the risk of myocardial infarction when both were taken. Another large study also found the risk to be increased in those taking regular rather than intermittent NSAID treatment with aspirin.[3] However, a study[4] involving 14 098 patients concluded that the risk of myocardial infarction was reduced in patients taking ibuprofen with aspirin when compared to those taking aspirin alone. Furthermore, a study[5] in 70 316 patients found that the risk of death in patients prescribed aspirin and ibuprofen was comparable to that of patients prescribed aspirin alone or with another NSAID.

The timing of doses may be important; a study[6] has shown that irreversible platelet aggregation occurred when a single daily dose of ibuprofen was given 2 hours after aspirin; however, when ibuprofen was given before aspirin as a single daily dose or given three times daily, platelet aggregation was reversible which may limit the cardioprotective effects of aspirin.

There are limitations to all these studies and further studies are needed before any recommendations can be made.[7-11]


1. MacDonald TM, Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. *Lancet* 2003; **361:** 573–4.
2. Kimmel SE, *et al.* The effects of nonselective non-aspirin nonsteroidal anti-inflammatory medications on the risk of nonfatal myocardial infarction and their interaction with aspirin. *J Am Coll Cardiol* 2004; **43:** 985–90.
3. Kurth T, *et al.* Inhibition of clinical benefits of aspirin on first myocardial infarction by nonsteroidal antiinflammatory drugs. *Circulation* 2003; **108:** 1191–5.
4. Patel TN, Goldberg KC. Use of aspirin and ibuprofen compared with aspirin alone and the risk of myocardial infarction. *Arch Intern Med* 2004; **164:** 852–6.
5. Curtis JP, *et al.* Aspirin, ibuprofen, and mortality after myocardial infarction: retrospective cohort study. *BMJ* 2003; **327:** 1322–3.
6. Catella-Lawson F, *et al.* Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001; **345:** 1809–17.
7. Etminan M, Samii A. Effect of ibuprofen on cardioprotective effect of aspirin. *Lancet* 2003; **361:** 1558–9.
8. Kimmel SE, Strom BL. Giving aspirin and ibuprofen after myocardial infarction. *BMJ* 2003; **327:** 1298–9.
9. Curtis JP, Krumholz HM. The case for an adverse interaction between aspirin and non-steroidal anti-inflammatory drugs: is it time to believe the hype? *J Am Coll Cardiol* 2004; **43:** 991–3.
10. Cheema AA. Should people on aspirin avoid ibuprofen? A review of the literature. *Cardiol Rev* 2004; **12:** 174–6.
11. Corman SL, *et al.* Impact of nonsteroidal antiinflammatory drugs on the cardioprotective effects of aspirin. *Ann Pharmacother* 2005; **39:** 1073–9.


**Spironolactone.** For the effect of aspirin in patients taking spironolactone, see p.1401.

## Pharmacokinetics

Aspirin and other salicylates are absorbed rapidly from the gastrointestinal tract when taken orally but absorption after rectal doses is less reliable. Aspirin and other salicylates can also be absorbed through the skin.

After oral doses, absorption of non-ionised aspirin occurs in the stomach and intestine. Some aspirin is hydrolysed to salicylate in the gut wall. Once absorbed, aspirin is rapidly converted to salicylate, but during the first 20 minutes after an oral dose aspirin is the main form of the drug in the plasma. Aspirin is 80 to 90% bound to plasma proteins and is widely distributed; its volume of distribution is reported to be 170 mL/kg in adults. As plasma-drug concentrations increase, the binding sites on the proteins become saturated and the volume of distribution increases. Both aspirin and salicylate have pharmacological activity although only aspirin has an anti-platelet effect. Salicylate is extensively bound to plasma proteins and is rapidly distributed to all body parts. Salicylate appears in breast milk and crosses the placenta.

Salicylate is mainly eliminated by hepatic metabolism; the metabolites include salicyluric acid, salicyl phenolic glucuronide, salicylic acyl glucuronide, gentisic acid, and gentisuric acid. The formation of the major metabolites, salicyluric acid and salicyl phenolic glucuronide, is easily saturated and follows Michaelis-Menten kinetics; the other metabolic routes are first-order processes. As a result, steady-state plasma-salicylate concentrations increase disproportionately with dose. After a 325-mg aspirin dose, elimination is a first-order process and the plasma-salicylate half-life is about 2 to 3 hours; at high aspirin doses, the half-life increases to 15 to 30 hours. Salicylate is also excreted unchanged in the urine; the amount excreted by this route increases with increasing dose and also depends on urinary pH, about 30% of a dose being excreted in alkaline urine compared with 2% of a dose in acidic urine. Renal excretion involves glomerular filtration, active renal tubular secretion, and passive tubular reabsorption.

Salicylate is removed by haemodialysis.


◊ References.

1. Needs CJ, Brooks PM. Clinical pharmacokinetics of the salicylates. *Clin Pharmacokinet* 1985; **10:** 164–77.


## Uses and Administration

Aspirin is a salicylate NSAID and has many properties in common with non-aspirin NSAIDs (p.99). Aspirin and other salicylates have analgesic, anti-inflammatory, and antipyretic properties; they act as inhibitors of the enzyme cyclo-oxygenase, which results in the direct inhibition of the biosynthesis of prostaglandins and thromboxanes from arachidonic acid (see p.2374). Aspirin also inhibits platelet aggregation; non-acetylated salicylates do not.

Aspirin is used for the relief of mild to moderate pain such as headache, dysmenorrhoea, myalgias, and dental pain. It has also been used in the management of pain and inflammation in acute and chronic rheumatic disorders such as rheumatoid arthritis, juvenile idiopathic arthritis, osteoarthritis, and ankylosing spondylitis. In the treatment of minor febrile conditions, such as colds or influenza, aspirin can reduce temperature and relieve headache and joint and muscle pains.

Aspirin is also used for its antiplatelet activity in the initial treatment of cardiovascular disorders such as angina pectoris and myocardial infarction and for the prevention of cardiovascular events in patients at risk. Other such uses include the treatment and prevention of cerebrovascular disorders such as stroke. For further details see under Antiplatelet Therapy, below.

Aspirin is usually taken by mouth. Gastric irritation may be reduced by taking doses after food. Various dosage forms are available including plain uncoated tablets, buffered tablets, dispersible tablets, enteric-coated tablets, and modified-release tablets. In some instances aspirin may be given rectally by suppository.

The usual oral dose of aspirin as an analgesic and antipyretic is 300 to 900 mg, repeated every 4 to 6 hours according to clinical needs, to a maximum of 4 g daily. The dose as suppositories is 450 to 900 mg every 4 hours to a maximum of 3.6 g daily.

Plasma-salicylate concentrations of 150 to 300 micrograms/mL are required for optimal anti-inflammatory activity (but see also Adverse Effects, above). Doses need to be adjusted individually to achieve optimum concentrations. Generally doses of about 4 to 8 g daily in divided doses are used for acute

rheumatic disorders such as rheumatoid arthritis or osteoarthritis. Doses of up to 5.4 g daily in divided doses may be sufficient in chronic conditions.

Indications for aspirin therapy in children are extremely limited because of the risk of Reye's syndrome (see under Adverse Effects, above), but include Kawasaki disease (see below), and juvenile idiopathic arthritis and Still's disease (see Rheumatic Disorders, below).

Sodium aspirin has also been used for the treatment of pain and fever.

**Administration in children.** Indications for aspirin therapy in children are extremely limited because of the risk of Reye's syndrome (see under Adverse Effects, above). For further information, including some doses, see Antiplatelet Therapy, Kawasaki Disease, and Rheumatic Disorders, below.

**Antiplatelet therapy.** Aspirin is an inhibitor of the enzyme cyclo-oxygenase, the **action** being considered to be due to an irreversible acetylation process.

- In blood platelets such enzyme inhibition prevents the synthesis of thromboxane $A_2$, a compound which is a vasoconstrictor, causes platelet aggregation, and is thus potentially thrombotic.
- In blood vessel walls the enzyme inhibition prevents the synthesis of prostacyclin, which is a vasodilator, has anti-aggregating properties, and is thus potentially anti-thrombotic.

Aspirin therefore appears to have paradoxical biological effects. The duration of these effects, however, may differ, with the *effects on the vascular tissue generally being shorter than the effects on the platelets* (although the *animal* species studied, the type of blood vessel used, and the prevailing experimental conditions may alter the results). The difference may be explained by the fact that vascular cells regain the ability to regenerate prostacyclin in a few hours but platelets are unable to re-synthesise cyclo-oxygenase, which results in no new thromboxane $A_2$ being produced for about 24 hours until more platelets are released by the bone marrow; as platelet activity in bone marrow may also be affected by aspirin it is generally considered that aspirin only needs to be given once daily for inhibition of platelet aggregation to occur. The inhibitory effect on thromboxane is rapid and unrelated to serum concentrations of aspirin, probably because of the inactivation of cyclo-oxygenase in platelets in the presystemic circulation. Since the effect is unrelated to systemic bioavailability, modified-release and dermal delivery preparations which do not achieve high systemic concentrations of aspirin are being developed to limit extraplatelet effects of aspirin. Inhibition is cumulative on repeated dosage, and it has been estimated that a daily dose of 20 to 50 mg will result in virtually complete suppression of platelet thromboxane synthesis within a few days. Large doses of 150 to 300 mg can produce maximum suppression almost instantaneously.

**Uses**. Aspirin's antiplatelet activity has led to its use for the treatment or prevention of a variety of disorders.[1-6]

- It is used as part of the initial **treatment** of unstable *angina* (p.1157) and is given in the early treatment of *myocardial infarction* (p.1175); it is also of benefit in the initial treatment of acute *ischaemic stroke* (p.1185).
- Aspirin is used for its combination of anti-inflammatory, antipyretic, and antiplatelet activity in the treatment of *Kawasaki disease* (see below). It is also used to treat thrombotic symptoms associated with *antiphospholipid syndrome*, such as occurs in patients with SLE (p.1513), and has been recommended for prophylactic use in pregnant patients with antiphospholipid antibodies who are at risk of fetal loss. The thrombolytic action of aspirin has also led to its use in thrombotic thrombocytopenic purpura (see Thrombotic Microangiopathies, p.1076). Aspirin has been tried in *pregnancy-induced hypertension* (see under Hypertension, p.1171) for the prevention of pre-eclampsia and intra-uterine growth retardation and may provide a small to moderate benefit in some women.
- It is of value for the **prevention** of cardiovascular events in patients at high risk, including those with stable or unstable angina, current or previous myocardial infarction, ischaemic stroke, or transient ischaemic attack (see Cardiovascular Risk Reduction, p.1164). It has also been used in the long-term management of atrial fibrillation (see under Cardiac Arrhythmias, p.1160) for the prevention of stroke in patients with contra-indications to warfarin or if there are no other risk factors for stroke.
- The value of aspirin for **primary prevention** of cardiovascular events, particularly *myocardial infarction* and *stroke* depends upon the accurate estimation of overall cardiovascular risk but is probably not justified in healthy individuals.[7-9]

  Although aspirin may prevent *venous thromboembolism* (p.1189) after surgery, other treatments have been preferred. However, it is recommended for use in preventing thrombotic complications associated with procedures such as angioplasty and coronary bypass grafting (see under Reperfusion and Revascularisation Procedures, p.1181). Aspirin is often given as an adjunct to patients with *peripheral arterial thromboembolism* (p.1178) to prevent propagation of the clot and also to prevent postoperative complications. It may have some effect in delaying disease progression and reducing vascular events in patients with *peripheral arterial disease* (p.1178) but an analysis[10] concluded that there was insufficient evidence to support its prophylactic use in patients with intermittent claudication but no additional cardiovascular risk factors.

  The benefit of aspirin for the primary prevention of cardiovascular events in patients with *diabetes mellitus* (see under Diabetic Complications, p.433) and who have no other cardiovascular risk factors remains to be determined.[8] Use is recommended in all those at increased risk, which includes (in the USA) all diabetics over 40 years of age,[11] or those aged 50 and over or with existing atherosclerosis or hypertension or a history of diabetes for over 10 years (in the UK).[12]

  The value of adding aspirin to anticoagulants for the prophylaxis of thromboembolism in patients with *prosthetic heart valves* (see p.1187) is also still to be firmly established. It is usually recommended as an adjunct in patients with other risk factors. Aspirin alone may be considered in patients with bioprosthetic valves who do not require anticoagulation.

Several pharmacological studies have attempted to find a **dose** of aspirin that would inhibit synthesis of platelet thromboxane $A_2$ while sparing the effect on prostacyclin production[13-15] but it has been pointed out[3] that in patients with vascular disease accompanying or caused by endothelial dysfunction, such as in atherosclerosis, a selective sparing of vascular prostacyclin production may not be obtained at any effective antiplatelet dose. However, the clinical relevance of inhibiting the synthesis of prostacyclin may have been exaggerated.[16] Experimental evidence indicates that aspirin is thrombogenic only at extremely high doses (200 mg/kg), far exceeding the minimum dose required to inhibit prostacyclin production. Also aspirin is clinically effective as an antithrombotic drug at doses that inhibit the synthesis of prostacyclin. Further support for the lack of importance of inhibition of prostacyclin synthesis comes from epidemiological studies in patients with arthritis given large doses of aspirin and patients with congenital cyclo-oxygenase deficiency; neither of these groups of patients have experienced an excess of thrombotic episodes.

In a meta-analysis conducted by the Antithrombotic Trialists' Collaboration[8] daily doses of 75 to 325 mg appeared to be equally effective for their antiplatelet effect; doses greater than 500 mg did not appear to be superior and caused more gastrointestinal adverse effects. Whether doses less than 75 mg offer the same efficacy with reduced gastrointestinal toxicity remains to be determined (see Effects on the Gastrointestinal Tract, above). The meta-analysis concluded that for the long-term prevention of serious vascular events in high-risk patients, a daily dose of aspirin in the range of 75 to 150 mg should be effective; if an immediate effect is required as in the initial treatment of acute myocardial infarction, acute ischaemic stroke, or unstable angina, a loading dose of 150 to 300 mg may be given. Other analyses[10,17] have made similar dose recommendations. However, another review[18] has suggested that doses as low as 75 or 80 mg daily may be inadequate for the primary prevention of stroke and myocardial infarction; it was considered that the most appropriate dose of aspirin for primary prevention was 160 mg daily. Aspirin should be chewed or dispersed in water; chewing a tablet of aspirin ensures that some buccal absorption occurs.

The use of aspirin in **children** is limited because of the risk of Reye's syndrome (see under Adverse Effects, above); however, it may be specifically indicated in those at risk of clot formation after cardiac surgery or for the prophylaxis of stroke in high-risk children. The *BNFC* has suggested oral doses of 1 to 5 mg/kg (up to a usual maximum of 75 mg) once daily in neonates and children up to 12 years of age; older children may be given 75 mg daily.


1. Patrono C. Aspirin as an antiplatelet drug. *N Engl J Med* 1994; **330:** 1287–94.
2. Lutomski DM, *et al.* Pharmacokinetic optimisation of the treatment of embolic disorders. *Clin Pharmacokinet* 1995; **28:** 67–92.
3. Schrör K. Antiplatelet drugs: a comparative review. *Drugs* 1995; **50:** 7–28.
4. Hung J. Aspirin for cardiovascular disease prevention. *Med J Aust* 2003; **179:** 147–52.
5. Saseen JJ. ASHP therapeutic position statement on the daily use of aspirin for preventing cardiovascular events. *Am J Health-Syst Pharm* 2005; **62:** 1398–1405.
6. Patrono C, *et al.* Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med* 2005; **353:** 2373–83.
7. Sanmuganathan PS, *et al.* Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. *Heart* 2001; **85:** 265–71.
8. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324:** 71–86. Correction. *ibid.*; 141.
9. Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. *Lancet* 2001; **357:** 89–95.
10. Eccles M, *et al.* North of England evidence based guideline development project: guideline on the use of aspirin as secondary prophylaxis for vascular disease in primary care. *BMJ* 1998; **316:** 1303–9.
11. American Diabetes Association. Aspirin therapy in diabetes. *Diabetes Care* 2004; **27** (suppl 1): S72–S73.
12. British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, The Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005; **91** (suppl V): v1–v52. Also available at: http://www.diabetes.org.uk/Documents/Reports/DiabetesUk_cardiovascular.pdf (accessed 08/12/06)
13. Patrignani P, *et al.* Selective cumulative inhibition of platelet thromboxane production by low-dose aspirin in healthy subjects. *J Clin Invest* 1982; **69:** 1366–72.
14. Weksler BB, *et al.* Differential inhibition by aspirin of vascular and platelet prostaglandin synthesis in atherosclerotic patients. *N Engl J Med* 1983; **308:** 800–5.
15. McLeod LJ, *et al.* The effects of different doses of some acetylsalicylic acid formulations on platelet function and bleeding times in healthy subjects. *Scand J Haematol* 1986; **36:** 379–84.
16. Hirsh J, *et al.* Aspirin and other platelet active drugs: relationship among dose, effectiveness, and side effects. *Chest* 1989; **95** (suppl 2): 12S–18S.
17. Campbell CL, *et al.* Aspirin dose for the prevention of cardiovascular disease: a systematic review. *JAMA* 2007; **297:** 2018–24.
18. Dalen JE. Aspirin to prevent heart attack and stroke: what's the right dose? *Am J Med* 2006; **119:** 198–202.


**Behçet's syndrome.** For reference to the use of aspirin in the management of vasculitic symptoms of Behçet's syndrome, see p.1499.

**Cataract.** Evidence to support or disprove the hypothesis that aspirin has a protective effect against cataract formation is considered inconclusive. A study in the US in over 22 000 males concluded that low-dose aspirin (325 mg on alternate days) for 5 years was unlikely to have a major effect on cataract formation but that a slightly decreased risk for cataract extraction could not be excluded.[1] In a later study[2] in the UK ophthalmic examination of over 1800 patients who were receiving 300 mg to 1.2 g of aspirin daily for transient ischaemic attacks failed to confirm any protective effect. Re-analysis[3] of the results of the original US study identified additional cases of cataract formation or extraction although these cases did not affect the overall conclusions of the original study. However, when the study patients were followed up over 15 years, observational data[4] suggested that the use of low-dose aspirin may, in fact, increase the risk of cataract development. It was considered that further trials were needed to establish the role of long-term aspirin in cataract prevention.


1. Seddon JM, *et al.* Low dose aspirin and risks of cataract in a randomised trial of US physicians. *Arch Ophthalmol* 1991; **109:** 252–5.
2. UK-TIA Study Group. Does aspirin affect the rate of cataract formation? Cross-sectional results during a randomised double-blind placebo controlled trial to prevent serious vascular events. *Br J Ophthalmol* 1992; **76:** 259–61.
3. Christen WG, *et al.* Low-dose aspirin and risk of cataract and subtypes in a randomized trial of U.S. physicians. *Ophthalmic Epidemiol* 1998; **5:** 133–42.
4. Christen WG, *et al.* Aspirin use and risk of cataract in posttrial follow-up of Physicians' Health Study I. *Arch Ophthalmol* 2001; **119:** 405–12.


**Dysmenorrhoea.** Drugs such as aspirin and other NSAIDs that inhibit prostaglandin production through inhibition of cyclo-oxygenase are effective drugs in the treatment of dysmenorrhoea (p.6).

**Fever.** Methods for controlling fever (see p.10) include the use of antipyretics and/or physical cooling methods (although the value of the latter is questionable). Paracetamol, salicylates such as aspirin, and some other NSAIDs are the main antipyretics used. However, salicylates are generally contra-indicated for the management of fever in children because of the possible link between their use and the development of Reye's syndrome (see under Adverse Effects, above).

**Headache.** Aspirin is often used for the symptomatic treatment of various types of headache including migraine (see p.616) and tension-type headache (see p.617). Aspirin given at the onset of symptoms can successfully treat an acute attack of migraine. However, absorption may be poor due to gastric stasis which is commonly present in migraine. For this reason dispersible and effervescent preparations and compound preparations containing drugs such as metoclopramide which relieve gastric stasis have been advocated.

References.


1. Tfelt-Hansen P, Olesen J. Effervescent metoclopramide and aspirin (Migravess) versus effervescent aspirin or placebo for migraine attacks: a double-blind study. *Cephalalgia* 1984; **4:** 107–11.
2. Buring JE, *et al.* Low-dose aspirin for migraine prophylaxis. *JAMA* 1990; **264:** 1711–13.
3. MacGregor EA, *et al.* Mouth-dispersible aspirin in the treatment of migraine: a placebo-controlled study. *Headache* 2002; **42:** 249–55.
4. Steiner TJ, *et al.* Aspirin in episodic tension-type headache: placebo-controlled dose-ranging comparison with paracetamol. *Cephalalgia* 2003; **23:** 59–66.
5. Lipton RB, *et al.* Aspirin is efficacious for the treatment of acute migraine. *Headache* 2005; **45:** 283–92.
6. Diener HC, *et al.* Aspirin in the treatment of acute migraine attacks. *Expert Rev Neurother* 2006; **6:** 563–73.


**Kawasaki disease.** Aspirin has been given in regimens with normal immunoglobulins to children with Kawasaki disease (p.2228) because of its anti-inflammatory, antipyretic, and antiplatelet activity.[1-4]

The usual practice is to use an anti-inflammatory regimen until the fever has settled and then convert to an antithrombotic regimen. The *BNFC* recommends an oral dose of 30 to 50 mg/kg

daily in 4 divided doses in children aged 1 month and over (neonates may be given 32 mg/kg daily in 4 divided doses); this should be continued until the patient is afebrile or for the first 14 days after the onset of symptoms. Once fever and signs of inflammatory disease resolve, the aspirin dose is reduced to 2 to 5 mg/kg daily (neonates may be given 5 mg/kg daily) as a single dose for its antiplatelet effect. Aspirin may be stopped 6 to 8 weeks after the onset of illness but is usually continued for at least one year if coronary abnormalities are present and is continued indefinitely if coronary aneurysms persist. Similar regimens[3,4] are used in the USA although the initial dose of aspirin is more usually 80 to 100 mg/kg daily.

Despite this widespread use the optimum dose and duration of treatment have not been clearly established, and the value of aspirin in the initial management of Kawasaki disease has been questioned. In a meta-analysis[5] fever duration was significantly shorter in those on high-dose aspirin; however, other studies[6] have not shown such a benefit. Meta-analyses[5,7] have also shown that the incidence of coronary artery abnormalities is not significantly different for regimens using high (over 80 mg/kg daily) or low doses of aspirin. Furthermore, a retrospective study[8] suggested that aspirin use (irrespective of dose) in the acute phase of the disease may be unnecessary as its addition to immunoglobulin treatment had no effect on the rate of coronary artery abnormalities. A more recent review[9] found that evidence from comparative studies failed to show that aspirin reduced the rate of coronary artery abnormalities; a lack of good quality randomised controlled trials prevented any recommendations on the use of aspirin in the treatment of Kawasaki disease.


1. Williams RV, *et al.* Pharmacological therapy for patients with Kawasaki disease. *Paediatr Drugs* 2001; **3:** 649–60.
2. Brogan PA, *et al.* Kawasaki disease: an evidence based approach to diagnosis, treatment, and proposals for future research. *Arch Dis Child* 2002; **86:** 286–90.
3. Newburger JW, *et al.* Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics* 2004; **114:** 1708–33. Correction. *ibid.* 2005; **115:** 1118. Also available at: http://pediatrics.aappublications.org/cgi/reprint/114/6/1708.pdf (accessed 12/04/07) Also published in *Circulation* 2004; **110:** 2747–71. Also available at: http://circ.ahajournals.org/cgi/reprint/110/17/2747.pdf (accessed 12/04/07)
4. Freeman AF, Shulman ST. Kawasaki disease: summary of the American Heart Association guidelines. *Am Fam Physician* 2006; **74:** 1141–8.
5. Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. *J Pediatr* 1997; **131:** 888–93.
6. Saulsbury FT. Comparison of high-dose and low-dose aspirin plus intravenous immunoglobulin in the treatment of Kawasaki syndrome. *Clin Pediatr (Phila)* 2002; **41:** 597–601.
7. Durongpisitkul K, *et al.* The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. *Pediatrics* 1995; **96:** 1057–61.
8. Hsieh K-S, *et al.* Treatment of acute Kawasaki disease: aspirin's role in the febrile stage revisited. *Pediatrics* 2004; **114:** 689. Full version: http://pediatrics.aappublications.org/cgi/reprint/114/6/e689 (accessed 27/11/06)
9. Baumer JH, *et al.* Salicylate for the treatment of Kawasaki disease in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 27/11/06).


**Leg ulcers.** A 4-month placebo-controlled study[1] in 20 patients suggested that aspirin 300 mg daily aided healing of chronic venous leg ulcers; the mechanism of action was unclear.[2] However, the validity of the findings has been challenged.[3] The management of leg ulcers is discussed on p.1585.


1. Layton AM, *et al.* Randomised trial of oral aspirin for chronic venous leg ulcers. *Lancet* 1994; **344:** 164–5.
2. Ibbotson SH, *et al.* The effect of aspirin on haemostatic activity in the treatment of chronic venous leg ulceration. *Br J Dermatol* 1995; **132:** 422–6.
3. Ruckley CV, Prescott RJ. Treatment of chronic leg ulcers. *Lancet* 1994; **344:** 1512–13.


**Malignant neoplasms.** For references to studies suggesting that regular use of aspirin and other NSAIDs may reduce the risk of developing malignant neoplasms of the gastrointestinal tract, see under NSAIDs, p.100.

**Myeloproliferative disorders.** Aspirin in low doses may be used to provide symptomatic relief for erythromelalgia (burning pain and erythema of the hands and feet) in patients with polycythaemia vera (p.654) and primary thrombocythaemia (p.654).

**Pain.** Aspirin, along with other NSAIDs and paracetamol, may be used for treating mild or moderate pain (see Choice of Analgesic, p.2) and is also used in moderate or severe pain to potentiate the effects of opioids. It is suitable for use in acute or chronic pain. Aspirin should not be used for pain relief in children because of its association with Reye's syndrome (see under Adverse Effects, above).

Dependence and tolerance are not a problem with non-opioid analgesics such as aspirin, but there is a ceiling of efficacy, above which increasing the dose has no further therapeutic effect.

References.


1. Edwards JE, *et al.* Single dose oral aspirin for acute pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1999 (accessed 27/11/06).
2. Hersch EV, *et al.* Over-the-counter analgesics and antipyretics: a critical assessment. *Clin Ther* 2000; **22:** 500–48.
3. Vergne P, *et al.* Aspirine, douleurs et inflammation. *Rev Med Interne* 2000; **21** (Suppl 1): 89s–96s.


**Rheumatic disorders.** Aspirin was once widely used in the treatment of rheumatoid arthritis (p.11) but has been superseded by better tolerated NSAIDs; however, juvenile idiopathic arthritis including Still's disease (p.10) are among the limited number of indications for aspirin use in children. The *American Hospital Service Formulary* suggests that children weighing 25 kg or less may be given an initial oral dose of 60 to 130 mg/kg daily in divided doses; heavier children should be started on 2.4 to 3.6 g daily. The usual maintenance dose is 80 to 100 mg/kg daily although up to 130 mg/kg daily may be required in some children; however, because of the risk of toxicity, it is recommended that children weighing over 25 kg should not receive doses of 100 mg/kg daily or above.

## Preparations

***BP 2008:*** Aspirin and Caffeine Tablets; Aspirin Tablets; Co-codaprin Tablets; Dispersible Aspirin Tablets; Dispersible Co-codaprin Tablets; Effervescent Soluble Aspirin Tablets; Gastro-resistant Aspirin Tablets;

***USP 31:*** Acetaminophen and Aspirin Tablets; Acetaminophen, Aspirin, and Caffeine Tablets; Aspirin and Codeine Phosphate Tablets; Aspirin Capsules; Aspirin Delayed-release Capsules; Aspirin Delayed-release Tablets; Aspirin Effervescent Tablets for Oral Solution; Aspirin Extended-release Tablets; Aspirin Suppositories; Aspirin Tablets; Aspirin, Alumina, and Magnesia Tablets; Aspirin, Alumina, and Magnesium Oxide Tablets; Buffered Aspirin Tablets; Butalbital and Aspirin Tablets; Butalbital, Aspirin, and Caffeine Capsules; Butalbital, Aspirin, and Caffeine Tablets; Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules; Carisoprodol and Aspirin Tablets; Carisoprodol, Aspirin, and Codeine Phosphate Tablets; Oxycodone and Aspirin Tablets; Pentazocine and Aspirin Tablets; Propoxyphene Hydrochloride, Aspirin, and Caffeine Capsules; Propoxyphene Napsylate and Aspirin Tablets.

**Proprietary Preparations** (details are given in Part 3)

***Arg.:*** Adiro†; Aspimed†; Aspirina; Aspirinetas; Ball†; Bayaspirina; Bufferin†; Cardioaspirina; Desenfriolito; Ecotrin; Geniol AP†; Geniol Prevencion; Geniol SC sin Cafeina; Geniolito†; Lacefal†; Lafeaspirina; Nuevapina; ***Austral.:*** Aspro; Astrix; Bex†; Cardiprin; Cartia; Disprin; Disprin Direct; Ecotrin†; Solprin; Spren†; Vincent's Powders†; ***Austria:*** Acekapton; Aspiricor; Aspro; ASS; Herz ASS; Herzschutz ASS; Salimont; Thrombo ASS; Thrombostad; Togal Mono; ***Belg.:*** Acenterine; Asaflow; Asarid†; Aspirine; Aspro; Cardioaspirine; Cardiphar; Dispril; Sedergine; Therasa†; ***Braz.:*** AAS; Aasedatil†; Aceticil; Analgesin; Antifebrin†; Ascedor†; Asetisin†; Aspirina; Bufferin; Caas†; Cardio AAS; Cimaas; Ecasil†; Hipotermal; Salicil; Salicin; Salitil; Somalgin; ***Canad.:*** Asaphen; Aspergum; Aspirin with Stomach Guard; Bufferin; Entrophen; Equate; Novasen; Rivasa; Tri-Buffered ASA; ***Chile:*** Aspirina; Cardioaspirina; Disgren; Ecotrin; Fluicor; Hassapirin Puro; Thrombo AS; ***Cz.:*** Acylpyrin; Anopyrin; Apo-Asa†; Aspro†; Godasal; Upsarin†; ***Denm.:*** Hjerdyl; Hjertemagnyl; Idotyl; Magnyl; ***Fin.:*** Aspirin Cardio; Aspirin Zipp; Disperin; Primaspan; ***Fr.:*** Aspirine; Aspirine pH8†; Aspirisucre; Aspro; Catalgine†; Claragine; ***Ger.:*** Acesal; Acetylin†; Aspro; ASS; Godamed; HerzASS; Miniasal; Santasal N; Thomapyrin akut†; Togal ASS; ***Gr.:*** Salospir; Upsalgin-N; ***Hong Kong:*** Aspilets; Astrix; Bokey; Cardiprin; Cartia; Disprin; Ecotrin; Glyprin; LAsprin; Propirin; ***Hung.:*** Aspirin Protect; Astrix; Colfarit; Istopirin†; Kalmopyrin; ***India:*** ASA; Aspicot; Colsprin; CV-Sprin; Delisprin; Disprin; Ecosprin; ***Indon.:*** Aptor; Ascardia; Aspilets; Astika; Bodrexin; Cardio Aspirin; Contrexyn; Farmasal; Inzana; Minigrip; Naspro; Procardin; Restor; Rheumapill; Thrombo Aspilets; ***Irl.:*** Aspro; Caprin; Disprin; Lowasa; Nu-Seals; Resprin; ***Israel:*** Acetosal; Alka-Seltzer; Ascriptin†; Buffered Pirin; Cartia; Ecoprin; Godamed; Micropirin; Tevapirin; ***Ital.:*** Acesal†; ASA-ratio; Ascriptin; Aspiglicina; Aspirina; Aspirina 03; Aspirinetta; Aspro; Bufferin†; Cardioaspirin; Cemirit; Kilios†; ***Malaysia:*** Aceprin; Bufferin Low Dose†; Cardiprin; Casprin; Disprin; Dusil†; Glyprin; ***Mex.:*** Acetil-A; Acetin; Acitab; Adiro†; Antacsal; ASA; Ascriptin; Aspirina Protect; Axal†; Disprina; Doloquim; Ecotrin; Midolen; Vastecel; ***Neth.:*** Asacard; Aspirine Protect; Aspro; Bisolgripin†; Darosal; Togal; ***Norw.:*** Albyl-E; Dispril; Globoid; ***NZ:*** Aspec; Aspro; Cardiprin†; Cartia; Disprin; Ecotrin; Solprin; ***Philipp.:*** Anthrom; Asaprin; Aspec; Aspilets; Cor-30, Cor-80; Cortal; Enteroprin; Tromcor; ***Pol.:*** Acard; Acesan; Alka-Prim; Alka-Seltzer; ASA; Aspimag; Aspirin Protect; Asprocard; Asprocol; Bestpirin; Calcipiryna; Cardiofil; Encopirin; Galocard; Nipas; Polocard; Polopiryna; Polopiryna S; Proficar; Upsarin; ***Port.:*** AAS; Asacard; ASP; Aspirina; Aspro†; Cartia; Melhoral Infantil†; Migraspirina; Salycilina†; Toldex; Tromalyt; ***Rus.:*** Aspinat Cardio (Аспинат Кардио); Aspirin Cardio (Аспирин Кардио); CardiASK (КардиАСК); Thrombo ASS (Тромбо АСС); ***S.Afr.:*** Disprin; Ecotrin; Myoprin; ***Singapore:*** Aspro; Astrix†; Bokey; Bufferin†; Cardiprin; Disprin; Dusil; Glyprin; ***Spain:*** AAS; Adiro; Aspinfantil†; Aspirina; Bioplak; Helver Sal†; Mejoral†; Okal; Orravina†; Rhonal; Saspryl†; Sedergine; Tromalyt; ***Swed.:*** Albyl minor; Bamycor†; Bamyl; Bamyl S; Emotpin†; Magnecyl; Trombyl; ***Switz.:*** ASA; Asperivo†; Aspirine Cardio; Aspro; ASS; Juridin; Thrombace Neo; Tiatral 100 SR; Togal ASS; ***Thai.:*** Actorin; Anassa; Asatab; Ascot†; Aspent; Aspilets; Asrina; Caparin; Cardiprin; Comoprin†; Entrarin; Seferin; V-AS; ***Turk.:*** Algo; Algo Bebe; Asabrin; Asinpirine; Aspapirine; Aspinal; Ataspin; Babyprin; Coraspin; Dispril; Ecopirin; Notras; Opon; ***UAE:*** Jusprin; ***UK:*** Alka; Angettes; Aspro; Caprin; Disprin; Disprin Direct; Enprin; Micropirin; Nu-Seals; PostMI†; Pure Health; ***USA:*** Adprin-B; Arthritis Pain Formula; Ascriptin; Aspergum; Asprimox†; Bayer Low Adult Strength; Bufferin; Buffex; Cama Arthritis Pain Reliever; Easprin; Ecotrin; Empirin; Extra Strength Bayer Plus; Genprin; Halfprin; Magnaprin†; Norwich Extra Strength; Norwich Regular Strength; Regular Strength Bayer; St. Joseph Adult Chewable; ZORprin; ***Venez.:*** Asaprol; Ascriptin; Aspiretina†; Azacard; Cardipirina; Coraspirina.

**Multi-ingredient:** numerous preparations are listed in Part 3.

# Auranofin *(BAN, USAN, rINN)*

Auranofiini; Auranofina; Auranofine; Auranofinum; Oranofin; SKF-39162; SKF-D-39162. (1-Thio-β-D-glucopyranosato)(triethylphosphine)gold 2,3,4,6-tetra-acetate.

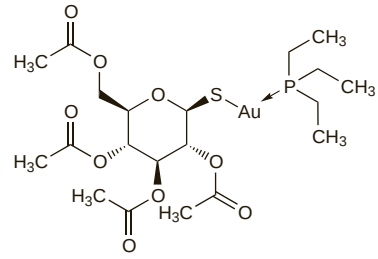
Ауранофин

$C_{20}H_{34}AuO_9PS$ = 678.5.

*CAS — 34031-32-8.*

*ATC — M01CB03.*

*ATC Vet — QM01CB03.*



## Adverse Effects and Treatment

The most common adverse effects of auranofin involve the gastrointestinal tract and include nausea, abdominal pain, and sometimes vomiting, but most often diarrhoea, which can affect up to 50% of patients and may be severe enough to cause patients to withdraw from treatment. Other adverse effects are similar to those experienced with sodium aurothiomalate (p.122), although they appear to be less troublesome since fewer patients stop treatment with auranofin than with injectable gold. As with other gold salts, treatment of adverse effects is generally symptomatic (see p.123). Modifying the diet to increase bulk, use of a bulking agent such as bran, or a temporary reduction in auranofin dosage, may help the diarrhoea (but see Effects on the Gastrointestinal Tract, below).

◊ Reviews.


1. Tozman ECS, Gottlieb NL. Adverse reactions with oral and parenteral gold preparations. *Med Toxicol* 1987; **2:** 177–89.


**Effects on the gastrointestinal tract.** Diarrhoea and abdominal pain are common with auranofin. The mechanism of gastrointestinal toxicity has not been established but may be associated with a reversible defect in intestinal permeability.[1] Although some have suggested that diarrhoea may occur in up to 50% of patients taking auranofin, a study in 269 patients given the drug for rheumatoid arthritis found that only about 15% experienced loose and watery stools over a six-month period.[2] Although bulking agents have been recommended in the management of auranofin-induced diarrhoea, no overall difference in incidence was seen between patients given prophylactic psyllium and those given placebo; however, patients given psyllium had slightly fewer days with loose and watery stools.

Gold-induced colitis has also been reported in patients taking auranofin.[3,4]


1. Behrens R, *et al.* Investigation of auranofin-induced diarrhoea. *Gut* 1986; **27:** 59–65.
2. van Beusekom HJ, *et al.* The moderate intestinal side effects of auranofin do not require prophylactic therapy with a bulkforming agent. Dutch Ridaura Study Group. *Clin Rheumatol* 1997; **16:** 471–6.
3. Michet CJ, *et al.* Auranofin-associated colitis and eosinophilia. *Mayo Clin Proc* 1987; **62:** 142–4.
4. Langer HE, *et al.* Gold colitis induced by auranofin treatment of rheumatoid arthritis: case report and review of the literature. *Ann Rheum Dis* 1987; **46:** 787–92.


**Effects on the kidneys.** In a retrospective review[1] of 1283 patients who had received auranofin for treatment of rheumatoid arthritis 41 (3.2%) were found to have developed proteinuria. In most cases proteinuria was treated by stopping auranofin therapy. Long-term follow-up of 36 patients indicated that proteinuria had resolved in 31 within 2 years and in 29 within 1 year. Seven of 8 patients later rechallenged with auranofin had no relapses. In a further review of 2 comparative double-blind studies using gold compounds in the treatment of rheumatoid arthritis, proteinuria was found to have developed in 27% (23 of 85) of patients treated with sodium aurothiomalate, in 17% (42 of 247) of those treated with auranofin, and in 17% (36 of 210) of those receiving placebo. All patients were receiving NSAIDs.


1. Katz WA, *et al.* Proteinuria in gold-treated rheumatoid arthritis. *Ann Intern Med* 1984; **101:** 176–9.


## Precautions

As for Sodium Aurothiomalate, p.123. Urine and blood tests should be carried out before starting au-