ulcer disease, or the prophylaxis of stress ulceration in children in intensive care (but see also under Bezoar Formation, above):

- 1 month to 2 years: 250 mg four to six times daily
- 2 to 12 years: 500 mg four to six times daily
- 12 to 18 years: 1 g four to six times daily

The oral suspension blocks fine-bore feeding tubes and tablets should be crushed and dispersed in water instead.

Gastrointestinal bleeding. Sucralfate is an effective drug for the prophylaxis and management of stress-induced gastrointestinal bleeding in severely ill patients but whether it should be chosen over an H_2-antagonist has been subject to debate. One study suggested it might reduce the risk of late-onset pneumonia compared with ranitidine.[1] Another study[2] found ranitidine to be more effective than sucralfate in reducing the risk of gastrointestinal bleeding; while there was a trend towards a lower rate of pneumonia among patients receiving sucralfate, the difference was not significant. However, meta-analyses[3] found an increased risk of pneumonia with ranitidine compared with sucralfate, but no difference in the rate of pneumonia with sucralfate and placebo; insufficient data were available to conduct a meta-analysis of sucralfate's efficacy in terms of rates of bleeding, and a re-assessment of recommendations for the prophylaxis of stress ulcers was called for. Later guidelines[4] concluded that the use of sucralfate did not influence the incidence of ventilator-associated pneumonia compared with placebo. For further discussion of stress ulceration and bleeding, including the use of sucralfate, see under Peptic Ulcer Disease, p.1702. There is also some evidence from a study[5] that sucralfate reduces gastrointestinal bleeding associated with NSAID use, although it does not prevent drug-induced gastric erosion.

In a study to assess whether oral prophylactic sucralfate could ameliorate the symptoms of acute radiation proctitis, sucralfate was found to increase the incidence of rectal bleeding compared with placebo; the cause of this increased bleeding was unclear.[6]

1. Prod'hom G, *et al.* Nosocomial pneumonia in mechanically ventilated patients receiving antacid, ranitidine, or sucralfate as prophylaxis for stress ulcer: a randomized controlled trial. *Ann Intern Med* 1994; **120:** 653–62.
2. Cook D, *et al.* A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. *N Engl J Med* 1998; **338:** 791–7.
3. Messori A, *et al.* Bleeding and pneumonia in intensive care patients given ranitidine and sucralfate for prevention of stress ulcer: meta-analysis of randomised controlled trials. *BMJ* 2000; **321:** 1103–6.
4. Dodek P, *et al.* Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. *Ann Intern Med* 2004; **141:** 305–13.
5. Hudson N, *et al.* Effect of sucralfate on aspirin induced mucosal injury and impaired haemostasis in humans. *Gut* 1997; **41:** 19–23.
6. Kneebone A, *et al.* The effect of oral sucralfate on the acute proctitis associated with prostate radiotherapy: a double-blind, randomized trial. *Int J Radiat Oncol Biol Phys* 2001; **51:** 628–35.

Gastro-oesophageal reflux disease. Although sucralfate has been tried for gastro-oesophageal reflux disease (p.1696) the results of studies have been inconsistent.[1-3] However, if lifestyle or dietary measures prove insufficient for the management of heartburn in pregnancy, sucralfate may be considered for first-line therapy.

1. Orlando RC. Sucralfate therapy and reflux esophagitis: an overview. *Am J Med* 1991; **91** (suppl 2A); 123S–124S.
2. Klinkenberg-Knol EC, *et al.* Pharmacological management of gastro-oesophageal reflux disease. *Drugs* 1995; **49:** 695–710.
3. Simon B, *et al.* Sucralfate gel versus placebo in patients with non-erosive gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1996; **10:** 441–6.

Mouth ulceration. Sucralfate has been investigated as a mouth rinse in the treatment and prophylaxis of stomatitis induced by cancer chemotherapy[1-3] although evidence of benefit for any drug is ambiguous (see Mucositis, p.640). One study[2] in 40 patients found a significant reduction in symptoms among 23 evaluable patients given sucralfate prophylactically. Seven patients withdrew due to aggravation of chemotherapy-induced nausea. It was suggested that to overcome this problem, the suspension should have a neutral taste, should not be swallowed after rinsing, and that rinsing should not be started until nausea had stopped. However, another study[4] involving 80 patients treated with fluorouracil for colorectal cancer found no significant difference in self-reported mucositis symptoms between patients given sucralfate suspension and those given placebo.

Sucralfate has also been reported to be of benefit in patients with recurrent aphthous stomatitis (mouth ulceration—p.1700). A study involving 21 such patients over 2 years found that topical application of sucralfate suspension 4 times daily was superior to treatment with an antacid (aluminium hydroxide with magnesium hydroxide) or placebo.[5]

In patients with Behçet's syndrome (p.1499), topical sucralfate suspension significantly decreased the frequency, healing time, and pain of oral ulceration, as well as the healing time and pain of genital ulceration,[6] when compared with placebo.

1. Pfeiffer P, *et al.* A prospective pilot study on the effect of sucralfate mouth-swishing in reducing stomatitis during radiotherapy of the oral cavity. *Acta Oncol* 1990; **29:** 471–3.
2. Pfeiffer P, *et al.* Effect of prophylactic sucralfate suspension on stomatitis induced by cancer chemotherapy: a randomized, double-blind cross-over study. *Acta Oncol* 1990; **29:** 171–3.
3. Allison RR, *et al.* Symptomatic acute mucositis can be minimized or prophylaxed [sic] by the combination of sucralfate and fluconazole. *Cancer Invest* 1995; **13:** 16–22.
4. Nottage M, *et al.* Sucralfate mouthwash for prevention and treatment of 5-fluorouracil-induced mucositis: a randomized, placebo-controlled trial. *Support Care Cancer* 2003; **11:** 41–7.
5. Rattan J, *et al.* Sucralfate suspension as a treatment of recurrent aphthous stomatitis. *J Intern Med* 1994; **236:** 341–3.
6. Alpsoy E, *et al.* The use of sucralfate suspension in the treatment of oral and genital ulceration of Behçet disease: a randomized, placebo-controlled, double-blind study. *Arch Dermatol* 1999; **135:** 529–32.

Skin ulceration. Sucralfate has reportedly been applied topically with some success to treat bleeding skin ulcers (p.1585) associated with malignancy,[1] and to promote the healing of venous stasis ulcers.[2] It has been suggested that sucralfate promotes angiogenesis by binding to, and preventing degradation of, basic fibroblast growth factor (bFGF).[2] Topical sucralfate 7% cream was also reported to decrease pain and speed healing of the wound after open surgical removal of haemorrhoids.[3]

1. Regnard CFB. Control of bleeding in advanced cancer. *Lancet* 1991; **337:** 974.
2. Tsakayannis D, *et al.* Sucralfate and chronic venous stasis ulcers. *Lancet* 1994; **343:** 424–5.
3. Gupta PJ, *et al.* Topical sucralfate decreases pain after hemorrhoidectomy and improves healing: a randomized, blinded, controlled study. *Dis Colon Rectum* 2008; **51:** 231–4.

Preparations

USP 31: Sucralfate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Antepsin; Netunal; Sucralmax; ***Austral.:*** Carafate; Ulcyte; ***Austria:*** Citogel; Sucralan; Sucralbene; Sucralstad†; Sucramed; Ulceral; Ulcogant; ***Belg.:*** Ulcogant; ***Braz.:*** Sucrafilm; ***Canad.:*** Novo-Sucralate; Sulcrate; ***Chile:*** Gastrocol†; Mulcatel; Sulcran; ***Cz.:*** Sucralan; Ulcogant; Venter; ***Denm.:*** Antepsin; Hexagastron; ***Fin.:*** Alsucral; Antepsin; ***Fr.:*** Keal; Ulcar; ***Ger.:*** Sucrabest; Sucraphil†; Ulcogant; ***Gr.:*** Peptonorm; Sucrate†; ***Hong Kong:*** Sucari; Ulsanic; ***Hung.:*** Alusulin; Ulcogant; Venter; ***India:*** Alfate; Sucrase; Ulcekon†; ***Indon.:*** Inpepsa; Musin; Neciblok; Ulcumaag; Ulsafate; Ulsicral; Ulsidex; ***Irl.:*** Antepsin; ***Israel:*** Ulsanic; ***Ital.:*** Antepsin; Citogel; Crafilm; Escudo; Gastrogel; Ipagastril†; Sucrager†; Sucral†; Sucralfin; Sucramal; Sucrate; Sucroril; Sugar; Sugast; Sunil; Ulcrast; Zenodian†; ***Jpn:*** Ulcerlmin; ***Malaysia:*** Alsucral; Ulcertec; ***Mex.:*** Apo-Lato; Unival; ***Neth.:*** Ulcogant; ***Norw.:*** Antepsin; ***NZ:*** Carafate; ***Philipp.:*** Iselpin; ***Pol.:*** Ulgastran; Venter; ***Port.:*** Calfate; Cinebil; Sucralum†; Ulcermate; Ulcermin; Ulcimer; ***Rus.:*** Venter (Вентер); ***S.Afr.:*** Ulcetab; Ulsanic; ***Singapore:*** Alsucral; Ulcertec; ***Spain:*** Gastral; Urbal; ***Swed.:*** Andapsin; ***Switz.:*** Ulcogant; ***Thai.:*** Sucraf-en†; Sucral; Sucrate†; Ulcefate; Ulcrafate; Ulsanic; ***Turk.:*** Antepsin; ***UAE:*** Sucralose; ***UK:*** Antepsin; ***USA:*** Carafate; ***Venez.:*** Dip; Exinol; Ulciram; Ulcon.

Multi-ingredient: ***Chile:*** Cicalfate; ***Fr.:*** Cicalfate; ***Gr.:*** Profenil†.

Used as an adjunct in: ***Ital.:*** Ketodol.

Sulfasalazine *(BAN, USAN, rINN)*

Salatsosulfapyridiini; Salazosulfapyridin; Salazosulfapyridine; Salazosulfapyridinum; Salicylazosulfapyridine; SI-88; Sulfasalatsiini; Sülfasalazin; Sulfasalazin; Sulfasalazina; Sulfasalazinas; Sulfasalazinum; Sulfasalazyna; Sulphasalazine; Szulfaszalazin. 4-Hydroxy-4′-(2-pyridylsulphamoyl)azobenzene-3-carboxylic acid.

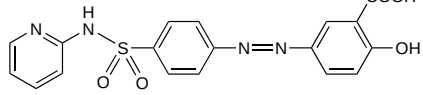
Сульфасалазин

$C_{18}H_{14}N_4O_5S$ = 398.4.

CAS — 599-79-1.

ATC — A07EC01.

ATC Vet — QA07EC01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.
Ph. Eur. 6.2 (Sulfasalazine). A bright yellow or brownish-yellow, fine powder. Practically insoluble in water and in dichloromethane; very slightly soluble in alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.
USP 31 (Sulfasalazine). A fine odourless bright yellow or brownish-yellow powder. Practically insoluble in water, in chloroform, in ether, and in benzene; soluble 1 in 2900 of alcohol, and 1 in 1500 of methyl alcohol; soluble in aqueous solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Since sulfasalazine is metabolised to sulfapyridine and 5-aminosalicylic acid (mesalazine), its adverse effects and precautions are similar to those of sulfonamides (see Sulfamethoxazole, p.340) and of mesalazine (p.1745). Many adverse effects have been attributed to the sulfapyridine moiety and appear to be more common if serum-sulfapyridine concentrations are greater than 50 micrograms/mL, if the daily dose of sulfasalazine is 4 g or more, or in slow acetylators of sulfapyridine.

The most commonly reported adverse effects include nausea and vomiting, abdominal discomfort, headache, fever, and skin rash.

Adverse effects can be broadly divided into 2 groups:

- dose-related effects are dependent on acetylator phenotype, and largely predictable; this group includes nausea and vomiting, headache, haemolytic anaemia, and methaemoglobinaemia
- hypersensitivity reactions are essentially unpredictable and usually occur at the start of treatment; this group includes skin rash, aplastic anaemia, hepatic and pulmonary dysfunction, and auto-immune haemolysis

Oligospermia, reversible on withdrawal of sulfasalazine, has also been reported. Sulfasalazine treatment may result in yellow-orange discoloration of skin, urine, and other body fluids. Some soft contact lenses may be stained.

Sulfasalazine should not be given to patients with a history of sensitivity to sulfonamides or salicylates. Use in children under 2 years of age is contra-indicated because of the risk of kernicterus.

Blood counts should be performed at the start of therapy and at least once a month for a minimum of the first 3 months of treatment. If a blood dyscrasia is suspected treatment should be stopped immediately and a blood count performed. Patients or their carers should be told how to recognise signs of blood toxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising or bleeding develop. Care is advisable in patients with G6PD deficiency because of the risk of haemolytic anaemia.

Sulfasalazine should be used with caution in hepatic or renal impairment. Liver function tests should be carried out at monthly intervals for the first 3 months of treatment. Periodic monitoring of kidney function has also been recommended.

◊ The adverse effects associated with the use of sulfasalazine in patients with inflammatory bowel disease[1] or rheumatoid arthritis have been reviewed.[2,3] The type and incidence of adverse effects appear to be similar in both groups of patients.[2] Although most reactions are minor and patients may continue therapy at the same or reduced dosage, some patients stop treatment because of adverse effects and in these cases a hyposensitisation regimen may be considered.[1,4,5] **Hyposensitisation** should not be attempted in patients with a history of a serious adverse effect such as agranulocytosis, toxic epidermal necrolysis, erythema multiforme, frank haemolysis, or a severe hypersensitivity reaction.[1,4,5] An alternative to hyposensitisation in patients with inflammatory bowel disease who cannot tolerate sulfasalazine is to try a drug that supplies the active 5-aminosalicylic acid component without sulfapyridine, as the latter is thought to be responsible for many of the adverse effects. Examples include balsalazide, mesalazine, and olsalazine; however, some patients still experience hypersensitivity, see under Mesalazine, p.1745.

1. Taffet SL, Das KM. Sulfasalazine: adverse effects and desensitization. *Dig Dis Sci* 1983; **28:** 833–42.
2. Amos RS, *et al.* Sulphasalazine for rheumatoid arthritis: toxicity in 774 patients monitored for one to 11 years. *BMJ* 1986; **293:** 420–3.
3. Farr M, *et al.* Side effect profile of 200 patients with inflammatory arthritides treated with sulphasalazine. *Drugs* 1986; **32** (suppl 1): 49–53.
4. Purdy BH, *et al.* Desensitization for sulfasalazine skin rash. *Ann Intern Med* 1984; **100:** 512–14.
5. Bax DE, Amos RS. Sulphasalazine in rheumatoid arthritis: desensitising the patient with a skin rash. *Ann Rheum Dis* 1986; **45:** 139–40.

Breast feeding. Small amounts of sulfasalazine and its sulfapyridine metabolites are excreted in breast milk; the concentrations of sulfasalazine and total sulfapyridine may be up to 30% and 50% of maternal serum concentrations respectively.[1] Bloody diarrhoea in a breast-fed infant whose mother was taking sulfasalazine 3 g daily has been reported.[2] The mother was a slow acetylator with a relatively high blood concentration of sulfapyridine, which contributed to the appearance of the drug in the infant's blood. Based on this report, the American Academy of Pediatrics[3] considers that sulfasalazine should be given with caution to breast-feeding mothers. However, others consider that continued treatment with sulfasalazine can generally be recommended to breast-feeding mothers of healthy infants.[4] A small study initially involving 17 mother-child pairs concluded sulfasalazine treatment could continue throughout pregnancy and lactation. The study found negligible amounts of sulfasalazine, and its main metabolite sulfapyridine, were transferred to the

child via breast feeding. The authors did however warn that this conclusion could not be applied to a prematurely born child or a child with haemolytic disease.[5]

1. Khan AKA, Truelove SC. Placental and mammary transfer of sulphasalazine. *BMJ* 1979; **2:** 1553.
2. Branski D, *et al.* Bloody diarrhea—a possible complication of sulfasalazine transferred through human breast milk. *J Pediatr Gastroenterol Nutr* 1986; **5:** 316–17.
3. 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 28/02/06)
4. Peppercorn MA. Sulfasalazine and related new drugs. *J Clin Pharmacol* 1987; **27:** 260–5.
5. Esbjörner E, *et al.* Sulphasalazine and sulphapyridine serum levels in children to mothers treated with sulphasalazine during pregnancy and lactation. *Acta Paediatr Scand* 1987; **76:** 137–42.

Effects on the blood. Blood disorders constitute 19% of all reactions reported with sulfasalazine.[1] As of June 1993 the UK CSM was aware of 191 reports of neutropenia, leucopenia, or agranulocytosis (22 fatal), 44 reports of bone marrow depression or aplastic anaemia (13 fatal) and 30 reports of thrombocytopenia (1 fatal).[1]

Although blood dyscrasias were initially thought to be caused by the sulfapyridine moiety, subsequent experience has shown that the aminosalicylates can also cause haematological reactions (see Mesalazine, p.1745). The risk of blood dyscrasias with sulfasalazine has been estimated at 0.6 per 1000 in those given the drug for inflammatory bowel disease, but about 10 times greater in patients receiving sulfasalazine for rheumatoid arthritis.[2]

Sulfasalazine inhibits folic acid absorption, interferes with its metabolism, and can increase folic acid requirements through haemolysis of red blood cells.[3,4] These effects are not usually significant in patients with inflammatory bowel disease unless there are additional factors causing folate deficiency, such as intercurrent illness or an exacerbation of bowel disease.[3,4] However, clinical folate deficiency with macrocytosis, megaloblastic anaemia, or pancytopenia has been reported rarely.[3,4] Macrocytic anaemia associated with sulfasalazine may occur more commonly in patients with rheumatoid arthritis; it was found in 7 of 50 patients within 3 to 4 months of starting treatment with sulfasalazine.[5] The effects of sulfasalazine on folic acid metabolism appear to be dose-related and respond to withdrawal or dosage reduction, and folic acid supplements;[3-5] intravenous folinic acid may sometimes be needed.[4] Although the effects may be potentially serious, they are not a contra-indication to continuing sulfasalazine treatment.[4,5]

Patients with a history of leucopenia associated with gold therapy for rheumatoid arthritis should not be given sulfasalazine since a similar reaction may occur.[6]

1. Committee on Safety of Medicines/Medicines Control Agency. Sulphasalazine and fatal blood dyscrasias. *Current Problems* 1993; **19:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024455&RevisionSelectionMethod=LatestReleased (accessed 02/07/08)
2. Committee on Safety of Medicines/Medicines Control Agency. Blood dyscrasias and mesalazine. *Current Problems* 1995; **21:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 16/06/06)
3. Swinson CM, *et al.* Role of sulphasalazine in the aetiology of folate deficiency in ulcerative colitis. *Gut* 1981; **22:** 456–61.
4. Logan ECM, *et al.* Sulphasalazine associated pancytopenia may be caused by acute folate deficiency. *Gut* 1986; **27:** 868–72.
5. Prouse PJ, *et al.* Macrocytic anaemia in patients treated with sulphasalazine for rheumatoid arthritis. *BMJ* 1986; **293:** 1407.
6. Bliddal H, *et al.* Gold-induced leucopenia may predict a similar adverse reaction to sulphasalazine. *Lancet* 1987; **i:** 390.

Effects on the cardiovascular system. Reports include Raynaud's syndrome with sulfasalazine[1] and myocarditis with sulfasalazine and with mesalazine.[2] Myocarditis leading to fatal cardiogenic shock has been reported in a patient receiving mesalazine and it has been recommended that sulfasalazine or mesalazine should be replaced by glucocorticoids if cardiac symptoms arise.[3]

1. Reid J, *et al.* Raynaud's phenomenon induced by sulphasalazine. *Postgrad Med J* 1980; **56:** 106–7.
2. Agnholt J, *et al.* Cardiac hypersensitivity to 5-aminosalicylic acid. *Lancet* 1989; **i:** 1135.
3. Kristensen KS, *et al.* Fatal myocarditis associated with mesalazine. *Lancet* 1990; **335:** 605.

Effects on fertility. Although successful pregnancies have been reported in the partners of men taking sulfasalazine,[1,2] male infertility is a well recognised complication of sulfasalazine treatment. Untreated inflammatory bowel disease is not associated with abnormal seminal quality or infertility, but oligospermia, reduced sperm motility, and an increase in morphological abnormalities are seen after treatment with sulfasalazine which may lead to infertility.[1-4] Oligospermia has been reported in 86% of men with inflammatory bowel disease treated with sulfasalazine.[1] Seminal characteristics and fertility return to normal within 2 to 3 months of withdrawing sulfasalazine and successful pregnancies have been reported after withdrawal.[1-3] The mechanism involved is thought to be a direct toxic effect on immature and developing spermatozoa, possibly due to the sulfapyridine moiety.[2-4] Improvement in seminal characteristics and successful pregnancies have been reported following substitution of mesalazine[4,5] or balsalazide[6] for sulfasalazine in patients with ulcerative colitis. However, reversible infertility, similar to that caused by sulfasalazine, has also been reported with mesalazine.[7]

1. Birnie GG, *et al.* Incidence of sulphasalazine-induced male infertility. *Gut* 1981; **22:** 452–5.
2. Riley SA, *et al.* Sulphasalazine induced seminal abnormalities in ulcerative colitis: results of mesalazine substitution. *Gut* 1987; **28:** 1008–12.
3. Toovey S, *et al.* Sulphasalazine and male infertility: reversibility and possible mechanism. *Gut* 1981; **22:** 445–51.
4. Ó'Moráin C, *et al.* Reversible male infertility due to sulphasalazine: studies in man and rat. *Gut* 1984; **25:** 1078–84.
5. Cann PA, Holdsworth CD. Reversal of male infertility on changing treatment from sulphasalazine to 5-aminosalicylic acid. *Lancet* 1984; **i:** 1119.
6. McIntyre PB, Lennard-Jones JE. Reversal with balsalazide of infertility caused by sulphasalazine. *BMJ* 1984; **288:** 1652–3.
7. Chermesh I, Eliakim R. Mesalazine-induced reversible infertility in a young male. *Dig Liver Dis* 2004; **36:** 551–2.

Effects on the gastrointestinal tract. Sulfasalazine-induced exacerbations of ulcerative colitis have been reported[1,2] and are probably caused by the salicylate moiety rather than sulfapyridine.[3] Other reported effects include intestinal villous atrophy.[4]

1. Schwartz AG, *et al*. Sulfasalazine-induced exacerbation of ulcerative colitis. *N Engl J Med* 1982; **306:** 409–12.
2. Ring FA, *et al.* Sulfasalazine-induced colitis complicating idiopathic ulcerative colitis. *Can Med Assoc J* 1984; **131:** 43–5.
3. Shanahan F, Targan S. Sulfasalazine and salicylate-induced exacerbation of ulcerative colitis. *N Engl J Med* 1987; **317:** 455.
4. Smith MA, *et al.* Angioimmunoblastic lymphadenopathy, sulphasalazine exposure and villous atrophy. *Postgrad Med J* 1985; **61:** 337–8.

Effects on the hair. Alopecia occurred on 2 occasions[1] after starting sulfasalazine 2 or 3 g daily in a patient with ulcerative colitis. On both occasions normal hair growth returned after treatment was stopped, and the patient was later successfully desensitised. However, alopecia that developed in another patient during sulfasalazine treatment did not recur on rechallenge.[2] In this case postpartum alopecia was considered to be the cause and these authors doubted whether sulfasalazine causes alopecia at all. Hair loss has been reported in 2 patients receiving mesalazine enemas.[3] However, remission of alopecia universalis has been reported during sulfasalazine treatment of rheumatoid arthritis.[4]

1. Breen EG, Donnelly S. Alopecia associated with sulphasalazine (Salazopyrin). *BMJ* 1986; **292:** 802.
2. Fich A, Eliakim R. Does sulfasalazine induce alopecia? *J Clin Gastroenterol* 1988; **10:** 466.
3. Kutty PK, *et al.* Hair loss and 5-aminosalicylic acid enemas. *Ann Intern Med* 1982; **97:** 785–6.
4. Jawad ASM, Scott DGI. Remission of alopecia universalis during sulphasalazine treatment for rheumatoid arthritis. *BMJ* 1989; **298:** 675.

Effects on the kidneys. UK licensed product information advises that adequate fluid intake and avoidance of urinary acidifiers may reduce the incidence of crystalluria and stone formation. For reports of nephrotic syndrome and of interstitial nephritis associated with sulfasalazine treatment, see under Mesalazine, p.1745.

Effects on the pancreas. The UK CSM had received 6 reports of pancreatitis associated with sulfasalazine as of February 1994.[1] There had been further reports associated with mesalazine (see p.1746). However, a large Danish population-based case-control study concluded neither sulfasalazine nor mesalazine was associated with an increased risk of pancreatitis, and that any increased risk might be associated with inflammatory bowel disease itself.[2]

1. Committee on Safety of Medicines/Medicines Control Agency. Drug-induced pancreatitis. *Current Problems* 1994; **20:** 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 02/07/08)
2. Munk EM, *et al.* Inflammatory bowel diseases, 5-aminosalicylic acid and sulfasalazine treatment and risk of acute pancreatitis: a population-based case-control study. *Am J Gastroenterol* 2004; **99:** 884–8.

Effects on the respiratory system. Although one study reviewed 50 cases of sulfasalazine-induced pulmonary complications, pulmonary toxicity remains a rare adverse effect.[1] Most reports include dyspnoea, cough, pulmonary infiltrates, fever, and eosinophilia, usually developing in the first few months of treatment although they may occur after several years.[1-3] Symptoms are generally readily reversible on withdrawal of sulfasalazine, although death due to fibrosing alveolitis has been reported,[2] and the need for corticosteroid therapy remains debatable.[1] These effects have also occurred with mesalazine, p.1746; they have been reported in patients with a history of sensitivity to salicylates, sulfonamides, or with no known sensitivity to these drugs.[2,3] Bronchiolitis obliterans organising pneumonia has been reported in a patient with rheumatoid arthritis receiving sulfasalazine;[4] clinical improvement occurred after sulfasalazine was stopped and corticosteroid therapy started.

1. Parry SD, *et al.* Sulphasalazine and lung toxicity. *Eur Respir J* 2002; **19:** 756–64.
2. Wang KK, *et al.* Pulmonary infiltrates and eosinophilia associated with sulfasalazine. *Mayo Clin Proc* 1984; **59:** 343–6.
3. Jordan A, Cowan RE. Reversible pulmonary disease and eosinophilia associated with sulphasalazine. *J R Soc Med* 1988; **81:** 233–5.
4. Ulubaş B, *et al.* Bronchiolitis obliterans organizing pneumonia associated with sulfasalazine in a patient with rheumatoid arthritis. *Clin Rheumatol* 2004; **23:** 249–51.

Effects on taste. Metallic taste has occurred in patients taking sulfasalazine for ulcerative colitis,[1] although diseases causing changes in gastrointestinal absorption may lead to zinc deficiency, which has itself been associated with a metallic taste. There has also been a report of two patients developing a reversible taste dysfunction, while taking sulfasalazine for rheumatoid arthritis.[2]

1. Ogburn RM. Sulfamethazine-related dysgeusia. *JAMA* 1979; **241:** 837.
2. Marcus RW. Sulfasalazine induced taste disturbances. *J Rheumatol* 1991; **18:** 634–5.

Lupus. A study in 11 patients with sulfasalazine-induced lupus found that induction of disease was more likely in patients who were slow acetylators of sulfapyridine, and who had HLA haplotypes associated with idiopathic SLE.[1] Furthermore, the risk of developing persistent SLE and lupus nephritis increased with duration of treatment and cumulative dose of sulfasalazine. Lupus-like syndrome has also occurred with mesalazine, see Lupus, p.1746.

1. Gunnarsson I, *et al.* Predisposing factors in sulphasalazine-induced systemic lupus erythematosus. *Br J Rheumatol* 1997; **36:** 1089–94.

Porphyria. Sulfasalazine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Pregnancy. Sulfasalazine and its sulfapyridine metabolites readily cross the placenta resulting in similar concentrations in the cord serum and maternal serum at delivery.[1,2] The concentration of the 5-aminosalicylic acid component of sulfasalazine in both cord serum and maternal serum is negligible.[1] There have been isolated reports of congenital abnormalities associated with use of sulfasalazine during pregnancy including coarctation of the aorta with a ventricular septal defect,[3,4] and genito-urinary disorders.[4] There is also a theoretical risk of kernicterus in the neonate if sulfasalazine is given close to delivery (see p.341). However, given the concentrations of sulfasalazine and its metabolites found in cord blood, the risk of kernicterus from maternal use is considered minimal.[2] There have been many successful and uncomplicated pregnancies during sulfasalazine therapy and the general consensus favours continuing sulfasalazine throughout pregnancy when indicated.[1,3-6] (See also Mesalazine, p.1746.) The minimum effective dose should be used and since sulfasalazine may precipitate folate deficiency (see Effects on the Blood, above), folic acid supplements are recommended.[7]

1. Khan AKA, Truelove SC. Placental and mammary transfer of sulphasalazine. *BMJ* 1979; **2:** 1553.
2. Järnerot G, *et al.* Placental transfer of sulphasalazine and sulphapyridine and some of its metabolites. *Scand J Gastroenterol* 1981; **16:** 693–7.
3. Hoo JJ, *et al.* Possible teratogenicity of sulfasalazine. *N Engl J Med* 1988; **318:** 1128.
4. Newman NM, Correy JF. Possible teratogenicity of sulphasalazine. *Med J Aust* 1983; **1:** 528–9.
5. Peppercorn MA. Sulfasalazine and related new drugs. *J Clin Pharmacol* 1987; **27:** 260–5.
6. Korelitz BI. Commentary: observations on sulfasalazine in Crohn's disease and ulcerative colitis. *J Clin Pharmacol* 1987; **27:** 265–6.
7. Byron MA. Treatment of rheumatic diseases. *BMJ* 1987; **294:** 236–8.

Interactions

Giving sulfasalazine with antibacterial therapy may reduce conversion of sulfasalazine to its active metabolite (see below).

Sulfasalazine has been reported to interfere with the absorption of digoxin (p.1262) or folic acid (see Effects on the Blood, above) from the gastrointestinal tract.

Antibacterials. Since the effects of sulfasalazine depend on release of 5-aminosalicylic acid by bacterial metabolism in the gut, any drug that reduces the intestinal microflora may reduce the production of active metabolite. Evidence for this has been seen in patients also given *rifampicin* and *ethambutol*,[1] or in subjects also given *ampicillin*.[2] However, a decrease in clinical effect does not seem to have been seen.

1. Shaffer JL, Houston JB. The effect of rifampicin on sulphapyridine plasma concentrations following sulphasalazine administration. *Br J Clin Pharmacol* 1985; **19:** 526–8.
2. Houston JB, *et al.* Azo reduction of sulphasalazine in healthy volunteers. *Br J Clin Pharmacol* 1982; **14:** 395–8.

Antineoplastics. For mention of 5-aminosalicylates such as sulfasalazine inhibiting the metabolism of thiopurine antineoplastics, and increasing their toxicity, see Mercaptopurine, p.744.

Pharmacokinetics

About 15% of an oral dose of sulfasalazine is absorbed from the small intestine, although some of this is subsequently returned to the intestine in bile via enterohepatic circulation. The great majority of the dose reaches the colon where the azo bond is cleaved by the action of the intestinal flora, producing sulfapyridine and 5-aminosalicylic acid (mesalazine). Results in patients who have undergone colectomy suggest that be-

tween 60 and 90% of the total dose is metabolised in this way, but the degree of metabolism depends both on the activity of the intestinal flora and the speed of intestinal transit; colonic metabolism is reduced in patients with diarrhoea (for example, in active inflammatory bowel disease).

The small amount of intact sulfasalazine that is absorbed is extensively protein bound and subsequently excreted unchanged in urine. It crosses the placenta and is found in breast milk.

After cleavage of the sulfasalazine molecule about 60 to 80% of available sulfapyridine is absorbed, and undergoes extensive metabolism by acetylation, hydroxylation, and glucuronidation. Peak steady-state concentrations of sulfapyridine are higher in slow acetylators than fast acetylators after similar doses and the former are 2 to 3 times more likely to have adverse effects. Some 60% of the original dose of sulfasalazine is excreted in urine as sulfapyridine and its metabolites. As with sulfasalazine, absorbed sulfapyridine crosses the placenta and is found in breast milk.

The 5-aminosalicylic acid (5-ASA) moiety is much less well absorbed. About one-third of liberated 5-ASA is absorbed and almost all of this is acetylated and excreted in urine. For further details of the pharmacokinetics of 5-aminosalicylic acid see under Mesalazine, p.1746.

◊ Reviews.

1. Klotz U. Clinical pharmacokinetics of sulphasalazine, its metabolites and other prodrugs of 5-aminosalicylic acid. *Clin Pharmacokinet* 1985; **10:** 285–302.

Uses and Administration

Sulfasalazine is a compound of a sulfonamide, sulfapyridine, with 5-aminosalicylic acid (mesalazine). Its activity is generally considered to lie in the 5-aminosalicylic acid moiety, which is released in the colon by bacterial metabolism, although intact sulfasalazine has some anti-inflammatory properties in its own right.

In inflammatory bowel disease (p.1697) it is used alone or as an adjunct to corticosteroids in the treatment of active ulcerative colitis and is effective in maintaining remission. Sulfasalazine may also be effective in the treatment of active Crohn's disease, particularly of the colon, but it does not appear to be of value in maintaining remissions. Sulfasalazine is also used as a disease modifying drug in the treatment of severe or progressive rheumatoid arthritis (below).

In **inflammatory bowel disease** the usual initial adult dose of sulfasalazine is 1 to 2 g orally 4 times daily in the UK. However, doses over 4 g daily are associated with an increased risk of toxicity, and in the USA, therefore, the usual dose is 1 g given 3 or 4 times daily, and an initial dose of 500 mg every 6 to 12 hours may be recommended to lessen gastrointestinal adverse effects. Enteric-coated tablets are also claimed to reduce the incidence of adverse gastrointestinal effects. The overnight interval between doses should not exceed 8 hours. On remission the dose in patients with ulcerative colitis is gradually reduced to 2 g daily and then generally continued indefinitely. For children 2 years of age or older doses should be proportional to body-weight; initially 40 to 60 mg/kg may be given daily in divided doses reduced to 20 to 30 mg/kg daily for the maintenance of remission.

Sulfasalazine is also given rectally, as suppositories, initially at a dose of 1 g at night and in the morning. After three weeks the dosage is gradually reduced according to response. Rectal sulfasalazine can be given as 0.5 to l g night and morning as an adjunct to treatment by mouth. Sulfasalazine may also be given by enema in a dose of 3 g at bedtime. The *BNFC* suggests the following daily dosage may be given in divided doses to children as suppositories according to age: 5 to 8 years old: 1 g; 8 to 12 years old: 1.5 g; 12 to 18 years old: 2 g. Enemas, to be retained for at least 1 hour, may be given at night in doses of 1 to 1.5 g for children aged 2 to 7 years, 1.5 to 2.25 g for children aged 7 to 12 years, and 3 g for children 12 to 18 years.

In adult **rheumatoid arthritis** treatment is usually started with an oral dose of 500 mg daily, as enteric-coated tablets, for the first week; dosage is then increased by 500 mg daily each week to a maximum of 3 g daily given in 2 to 4 divided doses according to tolerance and response. In the USA, sulfasalazine can also be used for polyarticular juvenile rheumatoid arthritis in children aged 6 years and older who have not responded adequately to salicylates or other NSAIDs. A dose of 30 to 50 mg/kg daily is given in two divided doses, to a maximum dose of 2 g daily. To reduce adverse gastrointestinal effects, an enteric-coated tablet is used and the initial dose should be a quarter to a third of the planned maintenance; it is then increased weekly to reach the maintenance dose after one month.

Although sulfasalazine is not licensed for juvenile rheumatoid arthritis in the UK, the *BNFC* suggests that children aged 2 to 18 years are given an initial oral dose of 5 mg/kg twice daily for 1 week. The dose is then increased to 10 mg/kg twice daily for 1 week, then 20 mg/kg twice daily for 1 week, and maintained on a dose of 20 to 25 mg/kg twice daily. For children aged 2 to 12 years the maximum dose suggested is 2 g daily, and for children aged 12 to 18 years 3 g daily.

Psoriasis. In a double-blind placebo-controlled study involving 50 patients with moderate to severe plaque-type psoriasis (p.1583), sulfasalazine 3 to 4 g daily produced a significantly greater clinical improvement than placebo after 4 weeks of treatment with a further improvement at 8 weeks.[1]

See also Psoriatic Arthritis, below.

1. Gupta AK, *et al.* Sulfasalazine improves psoriasis: a double-blind analysis. *Arch Dermatol* 1990; **126:** 487–93.

Pyoderma gangrenosum. Sulfasalazine is licensed in some countries for the treatment of pyoderma gangrenosum (p.1583), a condition that may be associated with inflammatory bowel disease, although published evidence of benefit is scanty.

References.

1. Shenefelt PD. Pyoderma gangrenosum associated with cystic acne and hidradenitis suppurativa controlled by adding minocycline and sulfasalazine to the treatment regimen. *Cutis* 1996; **57:** 315–9.

Rheumatoid arthritis. Sulfasalazine is considered to be a useful disease-modifying antirheumatic drug (DMARD) in the treatment of rheumatoid arthritis (p.11). Studies have found a beneficial clinical effect of sulfasalazine, compared with placebo, on tender and swollen joints, pain, and erythrocyte sedimentation rate.[1,2] Meta-analyses[3,4] of generally short-term comparative studies suggest that sulfasalazine is roughly comparable in efficacy to methotrexate, intramuscular gold (sodium aurothiomalate), and penicillamine. Other reviews[2,5] have also suggested that it may have similar efficacy to hydroxychloroquine and leflunomide. Although there are regional differences in the prescription of DMARDs, sulfasalazine has been widely used for initial therapy, especially of less severe disease.[5] In an open study[6] of 200 patients with rheumatoid arthritis who were randomly allocated to treatment with sulfasalazine or auranofin, 31% of the sulfasalazine recipients were still taking the drug after 5 years compared with 15% of auranofin recipients. Improvement over baseline was still significant at 5 years for those patients receiving sulfasalazine but not in those treated with auranofin. Although one study[7] failed to find convincing evidence that using sulfasalazine with methotrexate was more effective than either drug alone, other studies have shown that combination treatment with sulfasalazine plus methotrexate and hydroxychloroquine was more effective than methotrexate alone or with sulfasalazine or hydroxychloroquine or the combination of sulfasalazine with hydroxychloroquine.[8,9] A review of sulfasalazine use in the management of rheumatoid arthritis concluded that combination therapy may be of benefit in patients with early or advanced rheumatoid arthritis but that there is still a need for studies to determine the efficacy and tolerability of various combinations.[5]

1. Suarez-Almazor ME, *et al.* Sulfasalazine for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 28/02/06).
2. Weinblatt ME, *et al.* Sulfasalazine treatment for rheumatoid arthritis: a metaanalysis of 15 randomized trials. *J Rheumatol* 1999; **26:** 2123–30.
3. Felson DT, *et al.* The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. *Arthritis Rheum* 1990; **33:** 1449–61.
4. Capell HA, *et al.* Second line (disease modifying) treatment in rheumatoid arthritis: which drug for which patient? *Ann Rheum Dis* 1993; **52:** 423–8.
5. Plosker GL, Croom KF. Sulfasalazine: a review of its use in the management of rheumatoid arthritis. *Drugs* 2005; **65:** 1825–49.
6. McEntegart A, *et al.* Sulfasalazine has a better efficacy/toxicity profile than auranofin—evidence from a 5 year prospective, randomized trial. *J Rheumatol* 1996; **23:** 1887–90.
7. Dougados M, *et al.* Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. *Ann Rheum Dis* 1999; **58:** 220–5.
8. O'Dell JR, *et al.* Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med* 1996; **334:** 1287–91.
9. O'Dell JR, *et al.* Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; **46:** 1164–70.

Juvenile idiopathic arthritis. Juvenile idiopathic arthritis (p.10) is generally managed similarly to rheumatoid arthritis, but there is limited experience with the use of some antirheumatic drugs in children. Sulfasalazine has produced significant improvement in studies of patients with juvenile chronic arthritis; a literature review found that it was consistently reported to be of benefit.[1] Adverse effects were reported to be similar to those in adults, with the exception of a serum-sickness-like reaction which was mostly seen in systemic onset patients and may be unique to juvenile rheumatoid arthritis.[1]

1. Brooks CD. Sulfasalazine for the management of juvenile rheumatoid arthritis. *J Rheumatol* 2001; **28:** 845–53.

Spondyloarthropathies. ***Ankylosing spondylitis.*** Sulfasalazine has been found to be effective[1] in the treatment of active ankylosing spondylitis (p.13), but there is evidence that it is more useful in the treatment of active disease and peripheral articular manifestations than in the management of chronic long-standing disease.[2-4] The active moiety appears to be sulfapyridine rather than mesalazine.[5] Sulfasalazine was no better than placebo for the treatment of inflammatory back pain due to undifferentiated spondyloarthritis and early ankylosing spondylitis, but it was more effective than placebo in a subgroup of patients with no peripheral arthritis.[6]

1. Ferraz MB, *et al.* Meta-analysis of sulfasalazine in ankylosing spondylitis. *J Rheumatol* 1990; **17:** 1482–6.
2. Clegg DO, *et al.* Comparison of sulfasalazine and placebo in the treatment of ankylosing spondylitis: a Department of Veterans Affairs Cooperative study. *Arthritis Rheum* 1996; **39:** 2004–12.
3. Clegg DO, *et al.* Comparison of sulfasalazine and placebo for the treatment of axial and peripheral articular manifestations of the seronegative spondyloarthropathies: a Department of Veterans Affairs cooperative study. *Arthritis Rheum* 1999; **42:** 2325–9.
4. Chen J, Liu C. Sulfasalazine for ankylosing spondylitis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 28/02/06).
5. Taggart A, *et al.* Which is the active moiety of sulfasalazine in ankylosing spondylitis? A randomized, controlled study. *Arthritis Rheum* 1996; **39:** 1400–5.
6. Braun J, *et al.* Efficacy of sulfasalazine in patients with inflammatory back pain due to undifferentiated spondyloarthritis and early ankylosing spondylitis: a multicentre randomised controlled trial. *Ann Rheum Dis* 2006; **65:** 1147–53.

Psoriatic arthritis. A systematic review[1] of interventions for psoriatic arthritis (see p.13) concluded that sulfasalazine was one of only two drugs with published evidence of well proven efficacy in psoriatic arthritis (the other being high-dose parenteral methotrexate).

See also under Psoriasis, above.

1. Jones G, *et al.* Interventions for treating psoriatic arthritis. Available in The Cochrane Database of Systematic Reviews, Issue 3. Chichester: John Wiley; 2000 (accessed 29/04/05).

Preparations

BP 2008: Sulfasalazine Tablets;
USP 31: Sulfasalazine Delayed-release Tablets; Sulfasalazine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Azulfidine; Flogostop; ***Austral.:*** Pyralin; Salazopyrin; ***Austria:*** Colo-Pleon; Salazopyrin; ***Belg.:*** Salazopyrine; ***Braz.:*** Azulfin; Salazopirin; ***Canad.:*** Salazopyrin; SAS†; ***Chile:*** Azulfidine; ***Cz.:*** Salazopyrin; ***Denm.:*** Salazopyrin; ***Fin.:*** Salazopyrin; ***Fr.:*** Salazopyrine; ***Ger.:*** Azulfidine; Colo-Pleon; Pleon RA; ***Gr.:*** Salopyrine; ***Hong Kong:*** Salazopyrin; ***Hung.:*** Salazopyrin; ***India:*** Saaz; Salazar; Sazo; ***Indon.:*** Lazafin; Sulcolon; ***Irl.:*** Salazopyrin; ***Israel:*** Salazopyrin; ***Ital.:*** Salazopyrin; ***Jpn:*** Azulfidine; ***Malaysia:*** Salazopyrin; ***Mex.:*** Azulfidina; ***Neth.:*** Salazopyrine; ***Norw.:*** Salazopyrin; ***NZ:*** Salazopyrin; ***Pol.:*** Salazopyrin; ***Port.:*** Salazopirina; ***S.Afr.:*** Salazopyrin; ***Singapore:*** Salazopyrin; ***Spain:*** Salazopyrina; ***Swed.:*** Salazopyrin; ***Switz.:*** Salazopyrin; ***Thai.:*** Salazopyrin; Saridine; ***Turk.:*** Salazopryn; ***UK:*** Salazopyrin; Sulazine; ***USA:*** Azulfidine; ***Venez.:*** Azulfidine.

Sulglicotide *(BAN, rINN)*

Sulglicotida; Sulglicotidum; Sulglycotide.

Сульгликотид

CAS — 54182-59-1.
ATC — A02BX08.
ATC Vet — QA02BX08.

Profile

Sulglicotide is a sulfated glycopeptide with cytoprotective properties extracted from pig duodenum. It is used in the treatment of peptic ulcer disease (p.1702) and other gastrointestinal disorders in a usual oral dose of 200 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Gliptide; ***Venez.:*** Demucine†.