

DATA SHEET

Salazopyrin[®] and Salazopyrin[®] EN Tablets

Name of Medicine

Sulfasalazine

Presentation

Tablets, 500 mg (yellow, round, scored and marked '101' on one side, 'KPh' on reverse): 100's

EN-tabs, 500 mg (yellow, oval, enteric coated, marked '102' on one side, 'KPh' on reverse): 100's

Uses

Actions

Pharmacodynamics

Sulfasalazine has, among others, an immunosuppressive effect and has shown affinity to connective tissue. It has also been shown to have a wide range of effects in other biological systems. It is, however, difficult to judge the clinical relevance of its various pharmacological actions since the aetiology of rheumatoid arthritis is largely unknown. Moreover, the mode of action of sulfasalazine in the treatment of ulcerative colitis is also not known. A metabolite of the drug may have an inhibitory effect on an antigen-antibody process occurring in the intestinal wall and the salicylate component may act as an anti-inflammatory agent. The drug does not appear to have any long term antibacterial effect on the stool flora of patients with ulcerative colitis (see "Antibacterial Effect" below).

The following effects have been found *in vitro*: inhibition of bacterial growth; inhibition of prostaglandin synthesis; increased intestinal cytoprotection due to inhibition of prostaglandin degradation; reduction of leukotriene formation; modulation of polymorphonuclear leucocyte function; inhibition of proteolytic enzymes; inhibition of DNA synthesis; and impairment of folate absorption and metabolism.

Most of these effects have also been shown in experimental animal systems. This has led to the following alternative explanations of the clinical effects of sulfasalazine.

Antibacterial effect: West et al. (1974) found that the number of anaerobic bacteria in the colon lumen was markedly reduced by administration of sulfasalazine. Krook et al. (1981) showed that 1 month of sulfasalazine treatment gave a drastic reduction in the anaerobic bacteria count. After four months of continuing treatment the counts returned to normal, although a decrease in certain bacterial strains was still evident.

Rheumatoid arthritis may be an enteropathogenic arthritis. One well known observation is that experimental arthritis in pigs may be caused by *Clostridium perfringens* in the large bowel. Neumann et al. (1984) has recently examined the faecal flora in a normal control population and in rheumatoid arthritis patients during sulfasalazine treatment. During therapy there was a trend towards a decrease in the *Cl. perfringens* count in the sulfasalazine treated group which was not seen in the control group. Tremaine et al. (1984) have recently shown that patients on sulfasalazine have a significantly lower incidence of *Cl. difficile* infection than patients with no treatment, and that a significantly higher incidence of infection is observed after antibiotic therapy.

Anti-inflammatory and immunoregulatory effect: In recent years a large number of papers, predominantly on *in vitro* studies, have reported effects of sulfasalazine on the arachidonic acid metabolites, prostaglandins and leukotrienes.

Any equivalence to these effects *in vivo*, seen as an anti-inflammatory effect, has yet only partly been documented. Thus, inhibition of carrageenan inflammation could be demonstrated in the rat paw and in the rat colon. In the adjuvant arthritis model in rats, Steinwall et al. showed a significant inhibition at high doses of sulfasalazine. Indomethacin-induced ulceration could be reduced by sulfasalazine, and water transport was normalized by sulfasalazine both in human biopsy tissue and in the dinitrochlorobenzene (DNCB) colitis in rat model.

With regard to possible immunoregulatory effects, Holm and Perimann (1968) published a study on the effect of sulfasalazine upon lymphocytic activity. Sulfasalazine was shown to have a specific toxicity for lymphocytes, higher than for other cells. Campbell (1973) studied the effect of sulfasalazine in immunological models, and clear immunoregulatory effect was noted.

Laursen (1978) found that sulfasalazine in mice suppressed many immunological factors, such as serum levels of different immunoglobulins and the number of lymphocytes. Rubenstein et al. (1978) and Ali et al. (1982) have shown that sulfasalazine therapy depresses the activity of certain lymphocytes.

Pharmacokinetics

Absorption

After the administration of a single 2 g dose of Salazopyrin (enteric or non enteric coated tablets), sulfasalazine can be detected in serum within 6 hours: two days after administration the serum concentration is negligible. With repeated daily doses, the steady state serum level of sulfasalazine is achieved after 4 to 5 days.

Sulfasalazine is poorly absorbed from the small intestine (up to 30%), after which it is excreted into the bile. A few percent of the given dose is excreted unmetabolized into the urine. The unabsorbed drug is excreted in the faeces. This is also confirmed by the observation that around 70% of an ingested dose of sulfasalazine can be recovered in the effluent of ileostomised

patients. Sulfasalazine rapidly enters the enterohepatic circulation and is returned to the gastrointestinal tract via the biliary route. Up to 80% of the absorbed intact sulfasalazine can be recovered in the bile effluent.

Metabolism

The 70 to 80% of the ingested dose of intact sulfasalazine which reaches the colon is subjected to azo-reductive cleavage by the colonic flora to yield the two major metabolites, 5-amino-salicylic acid (5-ASA) and sulfapyridine. Sulfapyridine is rapidly absorbed, partly metabolized in the liver, primarily by acetylation, and subsequently excreted in the urine. Nonacetylated sulfapyridine is partly protein bound. The role of the gut bacteria in splitting sulfasalazine has been elucidated in detail by Peppercorn and Goldman (1972). Thus, the delay in appearance of sulfapyridine and 5-ASA in the serum after oral administration of sulfasalazine is consistent with the time taken for the drug to reach the microbially rich colon. The two products of cleavage, 5-ASA and sulfapyridine are subsequently metabolised.

In humans only N-acetyl-5-aminosalicylic acid has been identified as a metabolite of 5-ASA. Sulfapyridine metabolites have been identified in humans as: N⁴-acetylsulfapyridine; sulfapyridine-o-glucuronide; acetylsulfapyridine-o-glucuronide; 5-hydroxy-sulfapyridine-o-glucuronide; and N⁴-acetyl-5-hydroxy-sulfapyridine-o-glucuronide.

The rate at which sulfapyridine is acetylated in the liver is genetically determined. Patients can be readily classified as slow or fast acetylator phenotypes on the basis of the ratio of sulfapyridine and acetylsulfapyridine concentrations in serum or urine. There is also a genetic basis for differentiation of patients according to the rate at which sulfapyridine is hydroxylated. Those subjects who show relative slowness in acetylation and hydroxylation rates may be expected to show higher than normal serum concentration of sulfapyridine after administration of sulfasalazine.

Distribution and excretion

Intact sulfasalazine can be detected in serum within 6 hours after oral administration and between 2 and 10% of a single dose can be recovered as the unchanged molecule from the urine. No detectable sulfasalazine has been found in stools of normal subjects, although up to 7% of an orally administered sulfasalazine dose has been found in the faeces of patients having ulcerative colitis. Sulfasalazine and its metabolites excreted in the urine may impart an orange-yellow colour to alkaline urine.

Most of the 5-aminosalicylate moiety formed by bacterial action in the gut is excreted unchanged in the faeces. However, up to 33% of the salicylate absorbed can be recovered in the urine almost entirely as N-acetyl-5-aminosalicylic acid.

Both sulfasalazine and 5-ASA exhibit an affinity for collagen rich tissues. It has been shown that these two entities tend to concentrate primarily in the intestinal wall as well as in the peritoneal, pleural and synovial fluids. There is also evidence that blood borne sulfasalazine can enter the intestinal lumen directly from the serum, for it has been shown by Hannagren et al. (1973) that intravenously administered sulfasalazine concentrates intestinally in rats with ligated bile ducts.

The sulfapyridine formed by cleavage of sulfasalazine during azo-reduction by the intestinal flora is absorbed in the intestinal tract and appears to be evenly distributed in the various body

tissues and fluids. About two thirds of the amount of sulfapyridine present in sulfasalazine is excreted in the urine, partially as acetylated or glucuronidated metabolites. The faeces contain sulfapyridine equivalent to approximately 7% of the ingested dose. There is no detectable sulfapyridine in serum 3 days after termination of treatment.

Protein Binding

Greater than 95% of absorbed sulfasalazine is bound to serum proteins.

Indications

Ulcerative Colitis and Crohn's Disease: Adjunct in the treatment of ulcerative colitis with the usual supportive and dietary measures. For the management of severe, acute attacks of ulcerative colitis, rectal and systemic corticosteroid therapy appears to be clinically superior to sulfasalazine, but sulfasalazine may be more effective than corticosteroids in reducing the number of relapses in patients on maintenance therapy.

In the treatment of active Crohn's disease, especially in patients with colonic involvement.

Rheumatoid Arthritis: Salazopyrin EN-tabs are indicated for rheumatoid arthritis which has failed to respond to non-steroidal anti-inflammatory drugs (NSAIDs).

Dosage and Administration

The dosage of sulfasalazine should be individually adjusted according to the patient's tolerance and response to the treatment.

Inflammatory Bowel Disease

Salazopyrin or Salazopyrin EN-tabs (enteric coated) should be given preferably after meals in evenly divided doses over a 24 hour period with no more than 8 hours between overnight doses. The enteric coated tablets should not be crushed or broken.

Initial dosage

Adults: 1 to 2 g four times daily.

Children: 40 to 60 mg/kg bodyweight daily in three to six divided doses.

Maintenance dosage

Adults: 2 g daily in four divided doses.

Children: 40 mg/kg bodyweight daily in four divided doses. The daily maintenance dose should be continued unless contraindicated by side effects.

Salazopyrin EN-tabs may be used to minimise gastrointestinal intolerance to the drug.

Rheumatoid Arthritis

Oral: Two Salazopyrin EN-tabs, two or three times a day, i.e. 2 to 3 g daily. The enteric coated tablets should not be crushed or broken. For adults starting therapy, it is advisable to raise the daily dose according to the following schedule:

	1st WEEK	2nd WEEK	3rd WEEK	4th WEEK
Morning		1 tablet	1 tablet	2 tablets
Evening	1 tablet	1 tablet	2 tablets	2 tablets*
* etc. to 3 g/day maximum.				

At present no dosage recommendation regarding treatment with Salazopyrin EN-tabs in rheumatoid arthritis in children can be given.

Contraindications

Haematological, renal or hepatic dysfunction, allergic drug fever or skin eruptions due to sulphonamide derivatives including antibacterial sulphonamides, oral hypoglycaemics and thiazides.

Patients hypersensitive to sulfasalazine, its metabolites, or any other component of the product, sulfonamides, or salicylates.

Intestinal or urinary obstruction.

Patients with porphyria should not receive sulphonamides, as these drugs have been reported to precipitate an acute attack.

Children aged 2 years and younger.

Warnings and Precautions

Potential Toxicity: Deaths associated with the administration of sulfasalazine have been reported resulting from hypersensitivity reactions, agranulocytosis, aplastic anaemia, renal and liver damage, irreversible neuromuscular and CNS changes, and fibrosing alveolitis. The presence of clinical signs such as sore throat, fever, pallor, purpura or jaundice during sulfasalazine treatment may be indications of myelosuppression, hepatotoxicity, haemolysis or other serious blood disorders. The patient should be advised to report any untoward symptoms immediately. If serious toxic or hypersensitivity reactions occur, discontinue treatment with sulfasalazine immediately while awaiting the results of blood tests. Urticaria, other skin rashes and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids.

Monitoring for Toxicity: Sulfasalazine should be administered under constant medical supervision.

Complete blood counts (including differential white cell count) and liver function tests should be performed before starting sulfasalazine tablets and every second week during the first three months of therapy. During the second three months, the same tests should be done once monthly and thereafter once every three months, and as clinically indicated. Assessment of renal function (including urinalysis) should be performed in all patients initially and at least monthly for the first three months of treatment. Thereafter, monitoring should be performed as clinically indicated.

Reversible Male Infertility: Several recent reports have suggested that sulfasalazine may cause reversible infertility in males (Grieve, 1979; Levi et al., 1979; Toth, 1979; Traub et al., 1979; Toovey et al., 1981). Sulfasalazine therapy has been associated with a reduction in sperm counts, reduced sperm motility, morphologically abnormal sperm and an increased proportion of immature sperm. The mechanism by which sulfasalazine might affect sperm production is not understood. Until such time as this suggested association can be elucidated, a drug associated cause should be considered when investigating infertility in men taking sulfasalazine. Withdrawal of the drug usually reverses these effects within 2 to 3 months.

G-6-PD deficiency: Patients with a deficiency of erythrocytic glucose-6-phosphate dehydrogenase (G-6-PD) have been noted to develop haemolytic anaemia during treatment with sulfasalazine (Cohen et al., 1968; Gabor, 1973) and should be closely observed.

Hepatic or Renal Impairment, Blood Dyscrasias: Sulfasalazine should not be given to patients with impaired hepatic or renal function or with blood dyscrasias.

Folic Acid Metabolism: Oral sulfasalazine inhibits the absorption and metabolism of folic acid and may cause folic acid deficiency, potentially resulting in serious blood disorders (e.g. macrocytosis and pancytopenia) and possibly harming the foetus during pregnancy. (Also see Pregnancy and Lactation).

Fluid intake: Adequate fluid intake must be maintained in order to reduce the risk of crystalluria and stone formation.

Patients with Atopic Disease: Sulfasalazine should be given with caution to patients with history of atopic disease in view of the increased likelihood of hypersensitivity reactions in atopic patients, in particular those with a severe allergy or bronchial asthma.

Use in children: Use of sulfasalazine in children with systemic onset juvenile rheumatoid arthritis may result in a serum sickness-like reaction. Therefore, sulfasalazine is not recommended in these patients.

Interactions: Sulphonamides should be administered with caution to patients receiving other drug therapy (see Interactions).

Effect on ability to drive: Presumed to be safe or unlikely to produce an effect on the ability to drive or use machinery.

Pregnancy and Lactation

Australian Category A

Long-term clinical usage and experimental studies have failed to reveal any teratogenic or icteric hazards. Published data regarding use of sulfasalazine in pregnant women have revealed no evidence of teratogenic hazards. If sulfasalazine is used during pregnancy, the possibility of fetal harm appears remote. Oral sulfasalazine inhibits the absorption and metabolism of folic acid and may cause folic acid deficiency, potentially resulting in serious blood disorders (e.g., macrocytosis and pancytopenia) and possibly harming the foetus during pregnancy. Because the possibility of harm cannot be completely ruled out, sulfasalazine should be used during pregnancy only if clearly needed.

Use in lactation

The amount of sulfasalazine that passes into the maternal milk is negligible; however, the concentration of sulfapyridine in milk is about 40% of that in serum. Caution should be used, particularly if breastfeeding premature infants or those deficient in G-6-PD. The risk of kernicterus in breast-fed infants has been assessed as low with therapeutic doses, since sulfapyridine has been shown to have a poor bilirubin displacing capacity.

There have been reports of bloody stools or diarrhoea in infants of mothers on sulfasalazine who were breastfeeding. In cases where the outcome was reported, bloody stools or diarrhoea resolved in the infant after discontinuation of sulfasalazine in the mother.

As with all drugs, sulfasalazine should not be given to nursing mothers unless the expected benefits to the mother outweigh the potential risk to the infant.

Adverse Effects

Sulfasalazine shares the toxic potentialities of other sulphonamides, especially sulfapyridine, and the usual precautions of sulphonamide therapy should be observed. Moreover, it may be difficult to evaluate an adverse reaction in the individual case, since several of the untoward symptoms

and signs encountered in conjunction with treatment with sulfasalazine may be part of the disease. In assessing liver and joint complications, it should be borne in mind that such are often associated with ulcerative colitis.

The acetylation rate of sulfapyridine is determined by genetic factors. Slow acetylators can be expected to show higher serum levels of sulfapyridine, and thus may show an increased tendency towards adverse reactions.

Many side effects are dose dependent, and the symptoms can often be alleviated by reducing the dosage by greater subdivision of the dose.

The most common side effects are: nausea, vomiting and anorexia (which occur more frequently in patients receiving non-enteric coated sulfasalazine. To minimize the risk of gastrointestinal adverse reactions enteric coated tablets are used, which means that they do not disintegrate until they reach the small intestine); raised temperature; erythema and pruritus; headache; reversible oligospermia (oligospermia and infertility have been described in men treated with sulfasalazine. Withdrawal of the drug will reverse these effects).

The adverse reactions listed below have only seldom been reported, primarily in treatment of inflammatory bowel diseases and are typical of sulphonamides.

Infections and infestations: aseptic meningitis, pseudomembranous colitis.

Blood and lymphatic system disorders: red cell abnormalities* (e.g. haemolytic anaemia, macrocytosis), aplastic anaemia, megaloblastic anaemia, purpura, hypoprothrombinaemia, methaemoglobinaemia and bone marrow depression with leucopenia (e.g. agranulocytosis, thrombocytopenia), pancytopenia.

Immune system disorders: serum sickness.

Hypersensitivity reactions: anaphylactoid reactions, periorbital or facial oedema, conjunctival and scleral injection, allergic myocarditis and nephrotic syndrome.

Metabolism and nutrition disorders: anorexia.

Psychiatric disorders: mental depression.

Nervous system disorders: dizziness*, smell and taste disorders, peripheral neuropathy, headache, peripheral neuritis, convulsions, hallucinations, vertigo, insomnia, transient lesions of posterior column and transverse myelitis, encephalopathy.

Ear and labyrinth disorders: tinnitus*.

Cardiac disorders: pericarditis, cyanosis*.

Respiratory, thoracic and mediastinal disorders: lung complications (fibrosing alveolitis with e.g. dyspnoea, cough, eosinophilic infiltration), interstitial lung disease.

Gastrointestinal disorders: gastric distress*, abdominal pain*, diarrhoea, pancreatitis, stomatitis and impaired folic acid absorption, aggravation of ulcerative colitis.

Hepatobiliary disorders: hepatic failure, hepatitis fulminant, hepatitis (see PRECAUTIONS Section).

Skin and subcutaneous tissue disorders: toxic epidermal necrolysis (Lyell's syndrome), erythema multiforme (Stevens-Johnson syndrome), drug rash with eosinophilia and systemic symptoms (DRESS), toxic pustuloderma, alopecia, erythema, exanthema, exfoliative dermatitis, lichen planus, photosensitivity, pruritus, urticaria, generalised skin eruptions.

Musculoskeletal and connective tissue disorders: systemic lupus erythematosus, Sjögren's syndrome, arthralgia.

Renal and urinary disorders: proteinuria*, haematuria*, crystalluria*(see PRECAUTIONS Section), nephrotic syndrome, interstitial nephritis.

Reproductive system: reversible oligospermia (see PRECAUTIONS Section).

General disorders: fever, yellow discolouration of skin and body fluids*, petechiae and drug fever, periarteritis nodosum and LE phenomenon have occurred.

Investigations: induction of autoantibodies, elevation of liver enzymes.

(* indicates the effects are possibly dose-related).

Interactions

Sulphonamides may potentiate oral anticoagulants, methotrexate, and oral hypoglycaemics of the sulphonylurea type by displacing these drugs from their binding sites.

An increased incidence of gastrointestinal adverse events, especially nausea, has been reported with co-administration of oral sulfasalazine and methotrexate.

Increased sulphonamide blood levels may occur in patients who are receiving urinary acidifiers, oral anticoagulants, phenylbutazone, or oxyphenbutazone, indomethacin, sulphinpyrazone, or salicylates.

Decreased absorption of sulphonamides from the gastrointestinal tract may occur if antacids are given concurrently.

It has been reported that sulphonamides interfere with oral absorption of oxacillin and may inhibit the serum protein binding of penicillins.

Local anaesthetics which are derivatives of para-aminobenzoic acid may antagonise sulphonamide activity.

Reduced absorption of digoxin, resulting in non-therapeutic serum levels, has been reported when used concomitantly with oral sulfasalazine.

Folate deficiency may occur as sulfasalazine inhibits the absorption of folate.

Ferrous sulphate may impair the absorption of sulfasalazine however, the clinical significance of this interaction is doubtful.

Due to inhibition of thiopurine methyltransferase (TPMT) by sulfasalazine, bone marrow suppression and leucopenia have been reported when thiopurine 6-mercaptopurine or its prodrug, azothioprine, and oral sulfasalazine were used concomitantly.

Overdosage

The drug has low acute per oral toxicity in the absence of hypersensitivity. There is evidence that the incidence and severity of toxicity following overdosage are directly related to the total serum sulfapyridine concentration.

Symptoms: Similar to those of any sulphonamides. The most likely symptoms would be gastrointestinal disturbances (nausea, vomiting and abdominal pain), haematuria, crystalluria or anuria. In more advanced cases, central nervous system symptoms such as drowsiness, convulsions, etc., may be observed. Patients with impaired renal function are at increased risk of serious toxicity; treatment with sulfasalazine is contraindicated in these patients (see Contraindications). There are no documented reports of deaths due to ingestion of large single doses of sulfasalazine.

Treatment: There is no specific antidote and treatment is symptomatic and supportive. Alkalinize urine (2.5 to 4.0 g of sodium bicarbonate every 4 hours). If kidney function is normal, force fluids. If anuria is present, restrict fluids and salt and treat for renal failure. Sulfasalazine can be removed by haemodialysis. Catheterisation of the ureters may be indicated for complete renal blockage by crystals. For agranulocytosis discontinue the drug immediately, hospitalise the patient and institute appropriate therapy. Patients should be observed for development of methaemoglobinaemia or sulphaemoglobinaemia. If these occur, treat appropriately.

Pharmaceutical Precautions

Shelf life

5 years

Special Precautions for Storage

Store at or below 25°C

Medicine Classification

Prescription Medicine

Package Quantities

Salazopyrin Tablets 500 mg, available in HDPE bottles of 100 tablets.

Salazopyrin EN-Tablets 500 mg, available in HDPE bottles of 100 tablets.

Further Information

List of excipients:

The active ingredient in each tablet is sulfasalazine. Each tablet contains 500 mg sulfasalazine.

Salazopyrin tablets also contain: silica, magnesium stearate, maize starch.

Salazopyrin EN tablets also contain: silica, magnesium stearate, maize starch, cellacephate, propylene glycol, white beeswax, carnauba wax, glyceryl monostearate, macrogol 20000 and talc.

Salazopyrin tablets do not contain lactose, sucrose, or tartrazine.

Name and Address of Sponsor

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