PRODUCT MONOGRAPH

SULFINPYRAZONE

Sulfinpyrazone Tablets USP

200 mg

a) **Platelet Inhibitory Agent**
b) **Uricosuric agent**

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Control #: 138859

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THERAPEUTIC CLASSIFICATION

Platelet Inhibitory Agent

Uricosuric Agent

ACTIONS AND CLINICAL PHARMACOLOGY

i) In vitro experiments with SULFINPYRAZONE in human volunteers have demonstrated possible effectiveness in clinical states associated with abnormal platelet aggregation.

ii) Reduces serum urate level, prevents formation of new tophi, promotes resorption of existing tophi by increasing clearance of uric acid and water through the kidneys.

INDICATIONS AND CLINICAL USE

i) Inhibition of thrombotic and embolic processes associated with platelet adhesion, aggregation and reduced platelet survival time.

ii) Chronic phases of gout, both the intercritical or silent stage and the gouty arthritis stage.

CONTRAINDICATIONS

The safe use of sulfinpyrazone in pregnancy has not been established. It should not be used during pregnancy unless, in the opinion of the treating physician, the expected benefits outweigh the potential risks.

Active Peptic Ulcer.

Known hypersensitivity to sulfinpyrazone and other pyrazolone derivatives.

Severe hepatic or renal disease, unless due to platelet aggregates.

WARNINGS

Avoid salicylate therapy, unless administered under careful supervision:

i) Salicylates and citrates antagonize the uricosuric action of sulfinpyrazone and may therefore interfere with uric acid excretion.

ii) Salicylates may cause unpredictable, and, at times, serious prolongation of the bleeding time, and in combination with sulfinpyrazone, may cause bleeding episodes. If, during sulfinpyrazone therapy, aspirin or another chemically-related drug must be used, patients should be urged to report immediately any undue bleeding episode.

It should be administered with care to patients with a history of healed peptic ulcer.

A low incidence of acute renal failure in post-myocardial infarct patients receiving sulfinpyrazone has been reported. Rising BUN and serum creatinine levels and abnormal urine were prodromal. Results of renal biopsies were consistent with tubular necrosis or interstitial nephritis. The

condition reversed upon withdrawal of drug. Mechanism of action is not known, specific patients at risk cannot be identified. When sulfinpyrazone is used in post-myocardial infarct patients, frequent urinalyses and determination of BUN and serum creatinine should be done, especially during early drug treatment.

PRECAUTIONS

As with all pyrazole compounds, patients receiving SULFINPYRAZONE should be kept under close medical supervision and periodic blood counts are recommended.

Recent reports have indicated that sulfinpyrazone potentiates the action of sulfonamides, e.g., sulfadiazine, sulfisoxazole.

Other pyrazole compounds, e.g., phenylbutazone, potentiate the hypoglycemic effects of sulfonylureas. There have also been reports that phenylbutazone enhances the effects of insulin in diabetics.

Therefore, it is recommended that SULFINPYRAZONE be used with caution in conjuction with insulin, sulfonamides, the sulfonylurea hypoglycemic agents, and, in general, with agents known to displace or to be displaced by, other substances, such as penicillin, from serum albumin binding sites.

Because SULFINPYRAZONE is a potent uricosuric agent, it may precipitate urolithiasis and renal colic, especially in the initial stages of therapy, in hyperuricemic patients. For this reason, an adequate fluid intake and alkalinization of the urine are recommended. In cases with significant renal impairment, periodic assessment of renal function is indicated.

Since SULFINPYRAZONE modifies platelet behavior, and, therefore, interferes with one of the components of the blood-clotting system, it should be used with care in conjunction with certain Vitamin K antagonists which inhibit clotting through a different mechanism. Regular estimations of bleeding time should be performed.

ADVERSE REACTIONS

The most frequently reported adverse reactions to sulfinpyrazone have been gastric complaints or disturbances. SULFINPYRAZONE may aggravate or reactivate peptic ulcer. Gastrointestinal bleeding has been reported.

Skin rashes have been reported in rare instances. When they occur, the drug should be withdrawn.

Anemia, leukopenia, agranulocytosis, thrombocytopenia have rarely been associated with the administration of sulfinpyrazone.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms:

Nausea, vomiting, epigastric pain, ataxia, convulsions. Coma may follow convulsions.

Suggested Therapy:

No specific antidote. Induce emesis or gastric lavage, give symptomatic supportive treatment; intravenous glucose infusion. Analeptic therapy if respiration is affected.

DOSAGE AND ADMINISTRATION

Clinical states in which abnormal platelet behavior is an underlying causative factor.

Usual daily dose is 600-800 mg. It is recommended not to exceed 1000 mg (20 mg/kg for a 50 kg man) daily.

GOUT:

Usual daily dosage is 200-400 mg.

This average dosage may be increased up to 800 mg if necessary, or reduced to 200 mg when urate blood level has been satisfactorily controlled. Minimum effective dose should be maintained indefinitely without interruption even during acute attacks, which should be treated concomitantly with either phenylbutazone or colchicines.

The change from other uricosuric agents to SULFINPYRAZONE should be made at full dosage.

It is important to distribute the total dose as well as possible over the 24 hour period:

It is recommended that SULFINPYRAZONE be taken with meals.

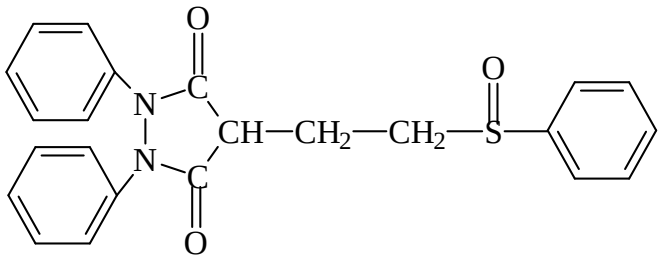
PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: Sulfinpyrazone

Chemical Name: 1, 2-diphenyl-4- (2-phenylsulfinylethyl)-3,5-pyrazolidinedione.

Structural Formula:



Molecular Formula: $C_{23}H_{20}N_2O_3S$

Molecular weight: 404.48

Description: The substance melts at 134-139ºC. It is white, odourless and somewhat bitter. It is easily soluble in ethyl acetate and chloroform, somewhat less in water, ethanol, ether, petroleum ether, mineral oils and fats. Inorganic and organic bases dissolve the substance to form enolate ions.

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AVAILABILITY OF DOSAGE FORMS

Each white, round, film-coated tablet, engraved ñ200ò on one side contains 200 mg sulfinpyrazone. Available in bottles of 100 and 500.

PHARMACOLOGY – SPECIFIC

Introduction:

SULFINPYRAZONE is an analogue of phenylbutazone and exhibits in man:

a) strong uricosuric, but virtually no anti-inflammatory properties;

b) a biological half-life of 3-8 hours, in spite of almost total binding to serum albumin;

c) low toxicity and minimal side effects at therapeutically effective dose levels.

The original Canadian observations showed that subjects with gout who were taking sulfinpyrazone as a uricosuric agent appeared to have a longer platelet survival and lower platelet turnover than untreated subjects. A large number of studies on pharmacological modifications of platelet function showed that sulfinpyrazone inhibits the "release" reaction. The release reaction is a response of platelets to a stimulus that leads to a loss of biologically-active material from platelets into the vascular bed. As release of these materials is essential for platelet aggregation and thrombus formation, inhibition of the release reaction will reduce or prevent these processes.

1. The Role of Platelets in the Pathogenesis of Cardiovascular Disease.

It follows that drugs which will reduce platelet aggregation might be useful in reducing the incidence of thrombosis in cardiovascular disease, particularly if atherosclerotic changes have occurred.

There is considerable experimental evidence that sulfinpyrazone inhibits thrombotic phenomena. Clinical data confirmed that inhibition of platelet function by sulfinpyrazone does reduce the incidence of thrombosis. Moreover, the clinical studies also indicated that SULFINPYRAZONE may be a useful drug for the treatment of certain thrombovascular disorders by virtue of its inhibitory effects on the interactions between platelets and surfaces.

Role of Platelets in Thrombosis:

When circulating mammalian platelets encounter a point of injury in the vessel wall, they adhere to the injured site. They are then transformed and through the release reaction, cause further platelets to adhere to them, leading to the formation of aggregates. The aggregates may be stable or unstable. Exposure to foreign surfaces can also cause these changes.

Many experimental studies have shown that the interaction of platelets with surfaces is important in the initiation of thrombosis. Interactions take place,

a) in association with vascular disease,

b) due to the presence of foreign materials.

a) Vascular Disease:

In the vessel wall collagen, or exposed basement membrane, are important stimuli to the development of platelet aggregates. Other factors include vascular injuries (which will show surface coatings of plasma components, e.g., gammaglobulins), intravascular stimuli (endotoxin), and perhaps, deposits leading to atherosclerosis. Disseminated intravascular coagulation belongs to this category.

b) Foreign Materials:

Foreign materials can be classified into circulating materials (e.g., antigen-antibody complexes or dextrans) and prosthetic materials, such as those used in vascular surgery for replacement or repair. The interactions between foreign materials and platelets are modified by certain plasma components, e.g. gammaglobulins.

Studies on Platelet Function:

The aggregation of platelets has been studied experimentally in great detail, particularly in vitro. It is not known to what extent the in vitro aggregation studies are applicable in vivo: within blood vessels.

It must be stressed that the multiple interactions that take place in the vascular bed are of prime importance and are difficult to duplicate in vitro.

Mustard and Packham[1] have reviewed the factors affecting platelet function. As transformation in connection with adherence, leading to the deposition of formed elements, is the major fate of platelets, the factors of importance to this process have been studied in detail.

A wide variety of biological materials (ADP, thrombin, certain other proteins, endotoxin, other particulate material, bacteria and viruses, certain fatty acids, catecholamines, serotonin, dextran, certain aromatic acids) leads to the release of platelet-ADP. ADP is not the only material released by the platelet in transformation. A large number of other substances of varying molecular size are released during the chain of reactions leading from platelet to thrombus. Nevertheless, ADP is the key substance in the process of aggregation. However, in animals and

man, ADP induced platelet aggregates are unstable if the coagulation process is abnormal; fibrin appears to be required to stabilize aggregates.[1]

Many methods for the assessment of platelet transformation (adhesion, aggregation, de-aggregation, "stickiness", "clumping", agglutination, fusion, etc.), are available.[2,3] Perhaps the most commonly used in vitro method is to measure the changes in light transmission through platelet-rich plasma in response to added stimuli and/or inhibitors. There are several techniques permitting the study in vivo of intra- and extra-vascular factors affecting platelet function.

Hemostasis, thrombosis, transfusion and transplantation are processes in which the pathophysiology of platelets is very important. In all of these, one is concerned with platelets interacting at an abnormal (accelerated) rate with connective tissue (collagen), ADP, and a normal or abnormal coagulation mechanism. The in vivo response of platelets to aggregating stimuli is determined by the quality (congenital or acquired defects) and the quantity (thrombocytopenia) of platelets.

The importance of platelets in thrombosis has been discussed in numerous reviews. [4,5] Platelets play a prime role in the formation of thrombi, the platelet count rising in the immediate post-operative period. The increased platelet count is paralleled by an increased percentage of adhesive platelets. While there appears to be a relationship between increased platelet adhesiveness, platelet survival and clinical manifestations of venous thrombo-embolic disease, probably only a small proportion of the occurring thrombo-emboli give rise to clinical manifestations.

Surgical patients with increased platelet "adhesiveness" had a smaller chance that their femoro-popliteal bypass grafts would remain patent.[6] Thus, a direct relationship between platelet adhesiveness in man and susceptibility of thrombus formation in flowing blood is suggested.

Nutritional studies suggest an association of high dietary fat with increased platelet adhesiveness and thrombotic tendency.[7] Other disorders associated with platelet abnormalities include gout and migraine. Patients with gout are susceptible to vascular disease complications; their platelets are more susceptible to surface effects and have a shortened survival and increased turnover.[8]

In vascular prosthetic surgery, thrombosis is a major problem. Much effort is being put into the production of "non-thrombogenic" materials and into studies aimed at inhibiting platelet aggregation and blood coagulation.

Platelets have been implicated in transplant rejection, particularly renal transplants.[9]

An interesting aspect of the role of platelets in thrombovascular disease is that of transient cerebral ischemic attacks, a condition which is characterized by reversibility. It demonstrates a correlation between platelet function and both vascular and neurological symptoms.

Platelets are only one of the many formed elements of blood and in all the conditions discussed, the influence of erythrocytes and other cells, as well as enzymes and other macromolecules, must be considered.[10]

2. Effects of SULFINPYRAZONE on Platelet Function

   Since the release of platelet constituents precedes aggregation, inhibition of the release reaction by sulfinpyrazone will prevent aggregation.[1]

Studies in man showed that sulfinpyrazone prolongs platelet survival and caused a significant decrease of platelet turnover.[11,22,28]

Subsequent studies in rabbits have demonstrated that sulfinpyrazone inhibits platelet aggregation that is induced by collagen, antigen-antibody complexes and gamma-globulin coated surfaces,[12] but not by adenosine diphosphate (ADP).[12]

Mustard, et al [13] found that pyrazole compounds inhibit platelet adherence to surfaces.[13]

These authors suggest that the mode of action with surface or particulate stimuli is through reducing platelet adherence to these stimuli. Pyrazole compounds prolong bleeding time in rabbits[12] and reduce the amount of deposit formed in extra-corporeal shunts.[14] Sulfinpyrazone blocks the thrombocytopenia that occurs with the rise in venous pressure and fall in arterial pressure when rabbits are given endotoxin.[15]

In rabbits, the administration of sulfinpyrazone[16] prolongs platelet survival to more than twice the normal time and reduces platelet turnover by nearly 50%.

There is evidence from studies in dogs that sulfinpyrazone inhibits or delays hyperacute renal allograft rejection.[17,18,19]

3. Clinical Use of Sulfinpyrazone as a Platelet-Active Agent.

In 1965, Smythe, et al[11] reported that sulfinpyrazone administered in a dose of 100 mg q.i.d. over a period of several weeks produced prolongation of platelet survival with reduced turnover. The changes in platelet survival and turnover were associated with reduced platelet

adhesiveness. These original observations have since been extended by Blakely et al.[20,21,29] Weily and Genton [22,28] and Evans.[23,24]

In Weily and Genton's[22] study, platelet survival time and platelet adhesiveness and aggregation were examined in 16 patients with prosthetic mitral valves. Subsequently, nine patients were treated with sulfinpyrazone in doses of 400 mg and 800 mg/day, and the platelet tests were repeated after a treatment period of 5 to 8 weeks. [51]Chromium survival time before treatment was shortened in 15 of the 16 patients, and the mean value for the entire group was 5.49 $\pm$ 0.23 days (normal 6.73 $\pm$ 0.21 days; $p < 0.001$). Mean platelet adhesiveness in glass bead columns was 52 $\pm$ 5% (normal, 30 to 60%). Platelet aggregation (Turbidometric technique of Born was normal). Treatment with 400 mg of sulfinpyrazone daily reduced platelet adhesivness to 40 $\pm$ 5% ($p<0.05$), but effected no change in platelet survival time or platelet aggregation. Therapy with 800 mg of sulfinpyrazone daily corrected platelet survival time to normal, 6.68 $\pm$ 0.57 days ($p<0.01$), but it produced no further decrease in adhesiveness and no change in aggregation. Weily and Genton[22] conclude that platelet abnormalities regularly occur in patients with prosthetic mitral valves and may contribute to thromboembolism in this group. Platelet survival time is a more sensitive measure of altered platelet kinetics than platelet adhesiveness or platelet aggregation. Therapy with 800 mg of sulfinpyrazone daily corrects demonstrated abnormalities and may be useful for prevention of thromboembolism in patients with prosthetic mitral valves.

Steele et al.[28] studied a group of 28 patients with idiopathic recurrent venous thrombosis. They found that platelet survival was significantly shortened in 18 patients who were also either refractory to anti-coagulants or had arterial thrombosis. Seven patients were selected for treatment with sulfinpyrazone. Subsequently, platelet survival time was shown to have increased in all seven patients, two returning to normal. No further episodes of thrombosis, arterial or venous, occurred during the 18-month treatment period.

Blakely et al.[21] and Blakely[29] reported that sulfinpyrazone, in doses sufficient to suppress platelet aggregation to collagen stimulus, was administered in a controlled, double-blind trial to a group of high-risk, elderly, male patients. 291 patients were included in the study for periods of up to 4 years. 125 patients without complications of atherosclerosis on entry showed a favourable and statistically-significant mortality trend in the treated group due to a reduction of deaths from vascular causes ($p< 0.05$). Examination of the sub-groups of patients with a history of stroke (99 patients) of myocardial infarction (60 patients) and peripheral vascular disease (47 patients) showed benefit on sulfinpyrazone treatment. In the first 2 groups, the differences in favour of the treated groups relative to deaths from vascular causes were significant with values of $p <0.0125$ and $p <0.025$, respectively. No differences were evident in the peripheral vascular disease group. The results support the view that sulfinpyrazone therapy reduces the imminence and frequency of vascular disease involving the cerebral and coronary vascular systems.

Evans[23,24] studied the use of platelet suppressive drugs on the incidence of recurrent venous thrombosis and transient cerebral ischemia. Patients presenting with recurrent venous thrombosis have been shown to have abnormal platelet function.

A controlled, randomized, double-blind study measured the effect of sulfinpyrazone on the incidence of recurrent venous thrombosis. In the 20 cases given placebo, eight developed further venous thrombosis compared with only three cases in the 30 given the active drug. The difference is statistically highly significant ($p<0.01$).

It is thought that most attacks of amaurosis fugax and transient cerebral ischemia are due to emboli, mainly composed of platelet aggregates arising from the areas of disturbed flow at the carotid bifurcation. In a controlled, double-blind, within-patient trial in 20 patients with symptoms of amaurosis fugax and with arterio-graphic evidence of carotid artery stenosis, sulfinpyrazone

800 mg daily reduced the incidence of recurrent venous thrombosis and for short-term reduction of thromboembolic complications associated with carotid artery stenosis.

Thrombosis in arteriovenous shunts is an important problem in hemodialysis. The effect of sulfinpyrazone on this complication was studied by Pineo et al.[30] in a controlled, double-blind, randomized trial. 52 patients undergoing chronic hemodialysis were included. It was observed that the incidence of clotting episodes was reduced four-fold by sulfinpyrazone from an untreated placebo level of 0.76 thrombi per patient-month to 0.18 thrombi per patient-month ($p<0.01$).

Blakely[31] investigated the effects of sulfinpyrazone on bleeding time in a group of 24 patients with atherosclerotic heart disease using the double-blind technique. He found that there was no significant difference between the placebo- and sulfinpyrazone-treated groups. In a group of 16 normal subjects, however, a significant difference at the 5% level was obtained.

4. Effects of SULFINPYRAZONE on Uric Acid Excretion:

   Sulfinpyrazone has strong uricosuric properties. Its pharmacological activity is to potentiate the urinary excretion of uric acid.[25,33,34] For this reason, it is useful for reducing the blood urate levels in patients with chronic tophaceous gout and acute intermittent gout, and for promoting the resorption of tophi. SULFINPYRAZONE is used in various stages of chronic gout, because of its potency and its continued effectiveness over prolonged periods of time.[33, 34] SULFINPYRAZONE may be effective in patients refractory to other uricosuric agents.

PHARMACOLOGY – GENERAL

Sulfinpyrazone administered either intraperitoneally, subcutaneously, or orally, inhibits formalin-induced acute inflammation in rats. This effect is somewhat less pronounced after hypo-

physectomy. In formalin-induced peritonitis and in dextran-induced edema in the rat paw, the anti-inflammatory effect of sulfinpyrazone is similar to that of aminopyrine. Sulfinpyrazone is less effective in other forms of experimental inflammation, such as serotonin edema, ultraviolet (epithelial) necrosis on the Selye granuloma-pouch in the rat, ultraviolet erythemia in the guinea pig, increased capillary permeability caused by dextran in rat skin, and histamine-conjecture of the vessels of the Krawkow-Pissemski isolated rabbit ear. [35,36,37]

Analgesic, Antipyretic Effects

The analgesic activity of the drug is slight, but can be clearly demonstrated in mice by the hotplate and tail-flick methods and in rabbits by means of electrical stimulation of the dental pulp. Sulfinpyrazone does not affect the pyrexia produced by injection of yeast in the rat.[35]

Metabolism:

Absorption from the human digestive tract is rapid and virtually complete. A short time after the intravenous injection of sulfinpyrazone the drug is no longer detectable in human plasma: the biological half-life in human serum is 3-8 hours. [27,32] In keeping with the short half-life, subdivision of the total daily dose is essential to ensure a reasonably constant blood level. 20-45% of the dose administered to human subjects is secreted unchanged in the urine in the course of 24 hours, most of it in the first 6 hours.[25, 26] The remainder is broken down into substances whose structures have not yet been completely elucidated.

Dayton et al.[27] found mainly sulfinpyrazone but also a hydroxylated metabolite, p-hydroxysulf-inpyrazone in human urine.

Retention of Electrolytes:

In doses of 200-800 mg per day, sulfinpyrazone causes no significant retention of sodium chloride or water in humans.[38, 39]

Human Tolerability:

The long-term tolerability of sulfinpyrazone has been assessed by Blakely [29] in a controlled, double blind trial of 291 patients.

113 patients on sulfinpyrazone and 139 on placebo experienced no untoward effects following treatment for mean periods of 23.2 and 22.7 months. 26 patients on sulfinpyrazone and 13 patients on placebo experienced adverse reactions. For those patients experiencing adverse effects on sulfinpyrazone, the most frequent were dyspepsia (5), skin rash (7), and gastro-intestinal blood loss (8). In the patients taking placebo, dyspepsia occurred in 2, skin rash in 3, and gastrointestinal blood loss in 2. Two deaths were reported to be due to gastrointestinal hemorrhage in the sulfinpyrazone group and one in the placebo group.

The slightly greater incidence of gastrointestinal problems in the sulfinpyrazone group could have been influenced by the greater usage of acetylsalicylic acid and acetylsalicylic acid-like compounds. Of the 26 patients in the sulfinpyrazone group who experienced adverse reactions, 21 were taking these compounds concurrently, as opposed to 8 of 13 on the placebo. Other unpublished studies confirm this low incidence of adverse reactions. Sulfinpyrazone is well tolerated over long periods of continuous therapy and is rarely associated with severe adverse reactions.

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