PRESCRIBING INFORMATION

RIVASA 80 mg EC

80 mg Tablets

(Acetylsalicylic acid delayed-release tablets, USP)

Analgesic and anti-inflammatory

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THERAPEUTIC OR PHARMACOLOGICAL CLASSIFICATION

Analgesic and anti-inflammatory

ACTION AND CLINICAL PHARMACOLOGY

ASA interferes with the production of prostaglandins in various organs and tissues through acetylation of the enzyme cyclo-oxygenase. Prostaglandins are themselves powerful irritants and produce headaches and pain on injection in man. Prostaglandins also appear to sensitize pain receptors to other noxious substances such as histamine and bradykinin. By preventing the synthesis and release of prostaglandins in inflammation, ASA may avert the sensitization of pain receptors.

INDICATIONS AND CLINICAL USE

RIVASA 80 mg EC is indicated for use in children only for rheumatic and arthritic pain under the supervision of a physician.

CONTRAINDICATIONS

Salicylate sensitivity, active peptic ulcer.

WARNINGS

ASA is one of the most frequent causes of accidental poisonings in toddlers and infants. Tablets should be kept well out of the reach of children.

Children and teenagers less than 18 years of age who have chicken pox, cold or flu symptoms should not take this medicine. ASA is reported to be linked to Reye's syndrome, a rare but serious illness.

PRECAUTIONS

Salicylates should be administered cautiously to patients with asthma and other allergic conditions, a history of gastrointestinal ulcerations; bleeding tendencies; significant anemia or hypoprothrombinemia.

Patients taking ASA daily are at an increased risk of developing gastrointestinal bleeding following the ingestion of alcohol.

Caution is necessary when salicylates and anticoagulants are prescribed concurrently, as salicylates can depress the concentration of prothrombin in the plasma.

Diabetics receiving concurrent salicylate and hypoglycemic therapy should be monitored closely; reduction of the sulfonylurea hypoglycemic drug dosage may be necessary; insulin requirements may change.

High doses (3g daily) of ASA during pregnancy may lengthen the gestation and parturition time.

Salicylates can produce changes in thyroid function tests.

Sodium excretion produced by spironolactone may be decreased by salicylate administration.

Salicylates in large doses are uricosuric agents; smaller amounts may depress uric acid clearance and thus decrease the uricosuric effects of other drugs.

Salicylates retard the renal elimination of methotrexate.

Salicylates may alter valproic acid (VPA) metabolism and may displace VPA from protein binding sites, possibly intensifying the effects of VPA. Caution is recommended when VPA is administered concomitantly with salicylates.

The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by the concomitant administration of ASA due to its indirect effect on the renin-angiotensin conversion pathway. The potential interaction may be related to the dose of ASA.

ADVERSE REACTIONS

Gastrointestinal: (the frequency and severity of these adverse effects are dose-related): nausea, vomiting, diarrhea, gastrointestinal bleeding and/or ulceration, dyspepsia, heartburn.
Ear: tinnitus, vertigo, hearing loss.

Hematologic: leukopenia, thrombocytopenia, purpura, anemia.

Dermatologic and hypersensitivity: urticaria, angioedema, pruritus, skin eruptions, asthma, anaphylaxis.

Miscellaneous: mental confusion, drowsiness, sweating, thirst.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

In mild overdosage these may include rapid and deep breathing, nausea, vomiting, vertigo, tinnitus, flushing, sweating, thirst, arid tachycardia. In more severe cases, acid-base disturbances including respiratory alkalosis and metabolic acidosis can occur. Severe cases may show fever, hemorrhage, excitement, confusion, convulsions or coma and respiratory failure.

Treatment

Treatment consists of prevention and management of acid-base and fluid and electrolyte disturbances. Renal clearance is increased by increasing urine flow and by alkaline diuresis but care must be taken in this approach to not aggravate further the metabolic acidosis that develops and the hypokalemia. Acidemia should be prevented by administration of adequate sodium containing fluids and sodium bicarbonate. Hypoglycemia is an occasional accompaniment of salicylate overdosage and can be managed by glucose solutions. If a hemorrhagic diathesis is evident, give vitamin K. Hemodialysis may be useful in complex acid base disturbances particularly in the presence of abnormal renal function.

DOSAGE AND ADMINISTRATION

RIVASA 80 mg EC: Dosage is as directed by a physician. The following mentioned guidelines can be used:

Children's dosage:

Under 6 years: as directed by a physician
6, 7 and 8 years: 4 tablets
9 and 10 years: 5 tablets
11 years and older: 6 tablets

Dosage may be repeated every 4 hours, not more than 5 times daily.

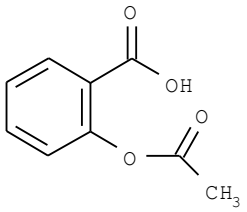
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Acetylsalicylic acid

Chemical Names: 2-(Acetyloxy) benzoic acid;
Salicylic acid acetate.

Structure:



Molecular Formula: $C_9H_8O_4$

Molecular Weight: 180.16 g/mol

Physicochemical Properties

Description: White granules, commonly tabular or needle-like, or white crystalline powder. Odorless or having a faint odor.

Solubility: Slightly soluble in water; freely soluble in alcohol; soluble in chloroform and ether; sparingly soluble in absolute ether.

pK value (25°C): 3.49

Melting Point: 135°C (rapid heating)

COMPOSITION

RIVASA 80 mg EC

Each tablet contains 80 mg acetylsalicylic acid as active ingredient.

Non-medicinal ingredients: Colloidal Silicon Dioxide, Glyceryl Stearate, Lactose Anhydrous, Methacrylic Acid Copolymer, Methylated Silica, Methylcellulose, Polydimethylsiloxane, Polysorbate, Pregelatinized Starch, Sodium Bicarbonate, Sodium Lauryl Sulfate, Stearic Acid, Sorbic acid, Sulfuric Acid, Talc, Titanium Dioxide and Triethyl Citrate.

AVAILABILITY OF DOSAGE FORM

RIVASA 80 MG EC

Each round, white enteric-coated tablet contains 80 mg acetylsalicylic acid. In packages of 1000 tablets.

STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature (15°-30°C).

PHARMACOLOGY

Absorption, distribution, metabolism and excretion

When ASA is taken orally, it is rapidly absorbed from the stomach and proximal small intestine. The gastric mucosa is permeable to the non-ionized form of acetylsalicylic acid, which passes through the stomach wall by a passive diffusion process.

Optimum absorption of salicylate in the human stomach occurs in the pH range of 2.15 to 4.10. Absorption in the small intestine occurs at a significantly faster rate than in the stomach. After an oral dose of 0.65 g ASA, the plasma acetylsalicylate concentration in man usually reaches a level between 0.6 and 1.0 mg in 20 minutes after ingestion and drops to 0.2 mg within an hour. Within the same period of time, half or more of the ingested dose is hydrolyzed to salicylic acid by esterases in the gastrointestinal mucosa and the liver, the total plasma salicylate concentration reaching a peak between one or two hours after ingestion, averaging between 3 and 7 mg. Many factors influence the speed of absorption of ASA in a particular individual at a given time; tablet disintegration, solubility, particle size, gastric emptying time, psychological state, physical condition, nature and quantity of gastric contents, etc., all affect absorption.

Distribution of salicylate throughout most body fluids and tissues proceeds at a rapid rate after absorption. Aside from the plasma itself, fluids which have been found to contain substantial amounts of salicylate after oral ingestion include spinal, peritoneal and synovial fluids, saliva and milk. Tissues containing high concentrations of the drug are the kidney, liver, heart and lungs. Concentrations in the brain are usually low, and are

minimal in feces, bile and sweat.
The drug readily crosses the placental barrier. At clinical concentrations, from 50% to 90% of the salicylate is bound to plasma proteins especially albumin, while acetylsalicylic acid itself is bound to only a very limited extent. However, ASA has the capacity of acetylating various proteins, hormones, DNA, platelets and hemoglobin, which at least partly explains its wide-ranging pharmacological actions.

The liver appears to be the principal site for salicylate metabolism, although other tissues may also be involved. The three chief metabolic products of ASA or salicylic acid are salicyluric acid, the ether or phenolic glucuronide and the ester or acyl glucuronide. A small fraction is also converted to gentisic acid and other hydroxybenzoic acids. The half-life of ASA in the circulation is from 13 to 19 minutes so that the blood level drops quickly after absorption is complete. However, the half-life of the salicylate ranges between 3.5 and 4.5 hours, which means that 50% of the ingested dose leaves the circulation within that time.

Excretion of salicylates occurs principally via the kidney, through a combination of glomerular filtration and tubular excretion, in the form of free salicylic acid, salicyluric acid, as well as phenolic and acyl glucuronides. Salicylate can be detected in the urine shortly after its ingestion but the full dose requires up to 48 hours for complete elimination. The rate of excretion of free salicylate is extremely variable, reported recovery rates in human urine ranging from 10% to 85%, depending largely on urinary pH. In general, it can be stated that acid urine facilitates reabsorption of salicylate by renal tubules, while alkaline urine promotes excretion of the drug.

Analgesia

The analgesic effect of ASA has been recognized and utilized clinically for more than half a century. The degree of analgesia attained with ASA is moderate but it has proved highly suitable in the management of pathological pain of mild to moderate severity. As regards site of action, both peripheral and CNS factors appear to contribute significantly to the pain relief afforded by ASA. As for mechanism of action, the accumulated evidence of recent years indicates that ASA acts by interfering with the synthesis and release of prostaglandins, thereby averting the sensitization of pain receptors to mechanical stimulation or to other mediators.

Anti-inflammatory effect

Components of the anti-inflammatory action of the salicylates are increased capillary resistance, thus reducing capillary leakage in response to local toxins, interference with the production of tissue-destructive lysosomal enzymes and inhibition of the synthesis of prostaglandin E compounds which have been shown to be potent mediators of the inflammatory process. Besides interfering with the synthesis of prostaglandins ASA also acts by interfering with lymphocyte activation and lymphokine production. Lymphokines are produced by activated thymus lymphocytes, which are abundant in the inflammatory tissues of patients suffering from rheumatoid arthritis. They cause increased vascular permeability and white blood cell chemotaxis, activate macrophages and stimulate lymphocyte DNA synthesis. They also induce release of tissue-destructive lysosomal

enzymes as well as prostaglandins. The prostaglandins themselves, beside causing many manifestations of inflammation also act as a potent negative feedback mechanism by inhibiting lymphokine production. An indepth review of the effects of ASA on the lymphocyte-macrophage axis in inflammation has recently been published.

TOXICOLOGY

The clinical and pathological signs of poisoning from toxic and lethal oral doses of ASA have been extensively described for man, much less extensively for other species.

The **acute toxicity** of ASA in animals has been studied and reviewed in detail by Boyd. The signs of poisoning in rats from doses in the lethal range are due to varying degrees of gastroenteritis, hepatitis, nephritis, pulmonary edema, encephalopathy, shock and minor toxic effects on other organs and tissues. Death is due to convulsions or cardiovascular shock. The major difference between species appears to be the ability to vomit toxic doses seen in man, cats and dogs, but not in mice, rats and rabbits. Otherwise, the pathological reaction to toxic doses of ASA is similar in all species in which such studies have been reported. The acute oral LD_{50} values have been reported as being over 1.0 g/kg in man, cat and dog, 0.92 g/kg in female and 1.48 g/kg in male albino rats, 1.19 g/kg in guinea pig, 1.1 g/kg in mouse and 1.8 g/kg in rabbit.

Chronic toxicity studies were reported in mice and rats. When ASA was administered at 2 to 20 times the maximum tolerated clinical dose to mice for up to one year, a dose-related deleterious effect was observed on mean survival time, number of young born and number of young raised to wearing age, no evidence of carcinogenic effect was found.

The chronic oral LD_{50} in male albino rats has been reported as 0.24g/kg/day when given for 100 days. At these daily doses ASA produced no anorexia and no loss of body weight. It did produce polydipsia, aciduria, diuresis, drowsiness, hyperreflexia, piloeraction, rapid and deep respiration, tachycardia, and during the second month, soft stools, epistaxis, sialorrhea, dacryorrhea and death in hypothermic coma. Autopsy disclosed the presence of a hypertrophied stomach, renal congestion, mild hepatitis and pneumonitis. While teratogenic effects were noted in animals at near lethal doses, there is no evidence to indicate that ASA is teratogenic in man.

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