PRODUCT MONOGRAPH

pms-ASA EC

(Acetylsalicylic Acid Delayed Release Tablets USP)

325 mg and 650 mg

Nonsteroidal Anti-inflammatory, Analgesic Agent

Platelet Aggregation Inhibitor

Pharmascience Inc.
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H4P 2T4

Date of Preparation:
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Control No.: 107504

PRODUCT MONOGRAPH

pms-ASA EC

Nonsteroidal Anti-inflammatory Analgesic Agent Platelet Aggregation Inhibitor

ACTION AND CLINICAL PHARMACOLOGY

pms-ASA EC (acetylsalicylic acid) has analgesic, antipyretic and anti-inflammatory properties.

In rheumatic diseases, although the analgesic and antipyretic effects are useful, the major purpose for which ASA is used is to reduce the intensity of the inflammatory process. Inhibition of prostaglandin synthesis may be involved in the anti-inflammatory action of ASA.

ASA also alters platelet aggregation and release reaction by inhibiting prostagiandin synthesis. Thromboxane A2 is an essential step in platelet aggregation. ASA prevents Thromboxane A2 formation by acetylation of platelet cyclooxygenase. This inhibition of prostaglandin synthesis is irreversible and affects platelet function for the life of the platelet.

The enteric coating substantially resists disintegration in aqueous fluids having a pH lower than 3.5 for a period of at least 2 hours and is capable of disintegrating in aqueous fluids having a pH of at least 5.5 in from 10 to 30 minutes. Thus, enteric coating effectively inhibits the release of ASA in the stomach, while allowing the tablet to dissolve in the upper portion of the small intestine for absorption from the duodenal area.

Clinical experience has shown that enteric-coated acetylsalicylic acid diminishes or eliminates gastric distress during long-term treatment with high doses of ASA.

Pharmacokinetic Information

Since pms-ASA EC are enteric-coated, the pharmacological effects are not immediate. Peak serum salicylate concentrations are reached 6 to 8 hours after single oral administration. This means that pms-ASA EC tablets are more useful for chronic administration as in arthritis, than for providing prompt relief of pain and fever.

The plasma half-life of salicylate concentrations is dose-dependent being 3 to 6 hours at low doses (325 mg to 1.3 g) and 15 to 30 hours at high doses.

INDICATIONS AND CLINICAL USE

pms-ASA EC is indicated whenever gastric intolerance to ASA is of concern.

pms-ASA EC is indicated for the relief of signs and symptoms of the following::

Osteoarthritis
Rheumatoid arthritis
Spondylitis Bursitis and other forms of rheumatism
Musculoskeletal disorders

Rheumatic fever, however, penicillin and other appropriate therapy should be administered concomitantly.

ASA is generally considered to be the primary therapy for most forms of arthritis.

Based on its platelet aggregation inhibitory properties, pms-ASA EC is indicated for the following:

- for reducing the risk of morbidity and death in patients with unstable angina and in those with previous myocardial infarction

- for reducing the risk of recurrent transient ischemic attacks (TIA) and for secondary prevention of atherothrombotic cerebral infarction,

CONTRAINDICATIONS

Sensitivity to the ingredients; active peptic ulcer. Patients who had a bronchospastic reaction to ASA or nonsteroidat anti-inflammatory drugs.

WARNINGS

ASA is one of the most frequent causes of accidental poisoning in toddlers and infants. pms-ASA EC should, therefore, be kept well out of the reach of all children.

PRECAUTIONS

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

Salicylates can produce changes in thyroid function tests.

Acute hepatitis has been reported rarely in patients with systemic lupus erythematosus and juvenile rheumatoid arthritis with plasma salicylate concentrations above 25 mg/100 mL. Patients have recovered upon cessation of therapy.

Regular daily use of alcohol while on ASA daily therapy may increase the risk of gastrointestinal bleeding.

Use in Pregnancy

ASA does not appear to have any teratogenic effects. ASA has been found to delay parturition in rats. This effect has also been described with nonsteroidal anti-intlammatory agents which inhibit prostagiandin synthesis.

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

Because of possible adverse effects on the neonate and the potential for increased matemal blood loss, ASA should be avoided during the last three months of pregnancy.

Use in Children

Recent studies have suggested that acetylsalicylic acid usage may cause the development of Reye's syndrome in children and teenagers with acute febrile illnesses, especially influenza and varicella. Although a direct causal relationship has not been established, it is recommended that salicylates be avoided when possible in children and teenagers with influenza or varicella.

Drug Interactions

Caution is necessary when pms-ASA EC and anticoagulants are prescribed concurrently, as ASA can depress the concentration of prothrombin in the plasma and may potentiate the action of anticoagulants.

Salicylates may potentiate sulfonylurea hypoglycemic agents. Large doses of salicylates may have a hypoglycemic action, and thus, affect the insulin requirements of diabetics.

Although salicylates in large doses are uricosuric agents, smaller amounts may depress uric acid clearance and thus decrease the uricosuric effects of probenecid, sulfinpyrazone and phenylbutazone.

Sodium excretion produced by spironolactone may be decreased in the presence of salicylates.

Salicylates also retard the renal elimination of rnethotrexate.

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

ADVERSE REACTIONS

Gastrointestinal:	nausea, vomiting, diarrhea, gastrointestinal bleeding and/or ulceration.
Ear:	tinnitus, vertigo, hearing loss.
Hematologic:	leukopenia, thrombocytopenia, purpura, anemia.
Dermatologic and Hypersensitivity:	urticaria, angioedema, pruritus, various skin eruptions, asthma and anaphylaxis.
Miscellaneous:	acute reversible hepatotoxicity, mental confusion, drowsiness, sweating and thirst.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

In mild overdosage these may include rapid and deep breathing, nausea, vomiting (leading to alkalosis), hyperpnea, vertigo, tinnitus, flushing, sweating, thirst and tachyeardia. (High blood levels of ASA lead to acid-base disturbances including respiratory alkalosis and metabolic acidosis.) Severe cases may show fever, hemorrhage, excitement, confusion, convulsions or coma, and respiratory failure.

Treatment

Treatment is essentially symptomatic and supportive. Administer water, universal antidote and remove by gastric lavage or emesis. Force fluids (e.g., salty broth) to replace sodium loss. If the patient is unable to retain fluids orally, the alkalosis can be treated by hypertonic saline intravenously. If salicylism acidosis is present, sodium bicarbonate intravenously is preferred because it increases the renal excretion of salicylates. Vitamin K is indicated if there is evidence of hemorrhage. Hemodialysis has been used with success.

Respiratory depression may require artificial ventilation with oxygen. Convulsions may best be treated by the administration of succinylcholine and artificial ventilation with oxygen. Central nervous system depressant agents should not be used.

Hyperthermia and dehydration are immediate threats to life and initial therapy must be directed to their correction and to the maintenance of adequate renal function. External cooling with cool water or alcohol should be provided quickly to any child who has a rectal temperature over 40˚C.

DOSAGE AND ADMINISTRATION

Dosage Adults: Single dose should not exceed 650 mg, to be repeated every 4 to 6 hours; the total daily dosage should not exceed 4,000 mg ASA unless otherwise advised by a physician, i.e, 12 tablets 325 mg, or 6 tablets 650 mg.

If the underlying condition requires continued use of pms-ASA EC for more than 5 days, a physician should be consulted.

Children: only as directed by a physician.

Analgesic; antipyretic

Patients should be advised not to exceed 4.0 g daily. Single doses should not be administered more frequently than every 4 hours.

Anti-inflammatory

Because the suppression of inflammation increases with the dose of salicylate even beyond the point of toxicity, the therapeutic objective is to employ as large a dose as possible short of toxicity. Most patients will tolerate blood salicylate levels in the range of 20 to 25 mg per cent. The most common reason for failing to obtain a therapeutic response to ASA is the administration of inadequate doses.

The generally accepted way to achieve effective anti-inflammatory salicylate blood levels of 20 to 25 mg per cent is to titrate the dosage by starting with 2.6 to 3.9 g daily, according to the size, age and sex of the patient. If necessary, the dosage is then gradually adjusted by daily increments of 0.65 g. Optimally, salicylate therapy should be monitored by periodic blood salicylate level determinations. If this is not practical, the appearance of auditory symptoms in the form of tinnitus or deafness are acceptable as an indication of the maximum tolerated salicylate dose.

In adults, the median dose at which tinnitus develops is 4.5 g per day, but the range extends from 2.6 to 6.0 g per day.

Intermittent administration is ineffective. Patients should be advised not to vary the dose from day to day depending on the level of pain because that often, fluctuates independently of the intensity of the inflammation. A continuous regimen of 0.65 g four times daily is considered to be minimum therapy for adults. pms-ASA EC should be administered four times daily. For night-time and early morning benefits, the last dose should be given at bedtime.

Once maintenance dose is established, pms-ASA EC 15 Maximum Strength may be useful to encourage patient compliance.

There is an inverse relation between blood salicylate levels at which auditory symptoms appear and the age of the patient. In the young adult, this is usually in the range of 20 to 30 mg per cent. In children, however, the level may be much higher, or the effect apparently absent. Because salicylate toxicity may appear without such warning in children, the usual practice is to give ASA in a daily dose of 50 to 80 mg per kilogram of body weight and to follow blood levels aiming for a concentration of about 30 mg per cent.

Rheumatic Fever

A total daily dosage of 80 mg per kilogram of body weight administered in divided doses to allay the pain, swelling and fever.

Platelet Aggregation Inhibitor

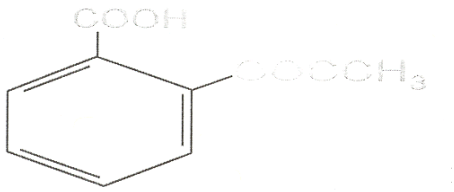
Patients with unstable angina or previous myocardial infarction: 325 mg daily or every second day, depending on the individual needs of the patient as directed by a physician. Therapy to continue indefinitely.
Patients with recurrent transient ischemic attacks (TIA) and for secondary prevention of atherothrombotic cerebral infarction: 325 mg daily or every second day, depending on the individual needs of the patient as directed by a physician. Therapy to continue indefinitely.

PHARMACEUTICAL INFORMATION

Drug Substance

Trade Name: pms-ASA EC
Common Name: Acetylsalicylic Acid (ASA)
Chemical Name: Salicylic acid acetate

Structural Formula of Acetylsalicylic Acid:



Molecular formula: $C_9H_8O_4$

Molecular weight: 180.16

AVAILABILITY OF DOSAGE FORMS

pms-ASA EC (Acetylsalicylic Acid Delayed Release 325 mg Tablets, USP) contain 325 mg of acetylsalicylic acid, enteric-coated. Round, brown, film-coated tablets. Supplied in bottles of 1000 (for dispensing use only).

pms-ASA EC (Acetylsalicylic Acid Delayed Release 650 mg Tablets, USP) tablets contain 650 mg of acetylsalicylic acid, enteric-coated. Oval, orange, film-coated tablets. Supplied in bottles of 1000 (for dispensing use only).

Composition

Following is the list of non-medicinal ingredients:

325 mg tablets: Microcrystalline cellulose, Guar gum, Corn starch, Hydrogenated vegetable oil type I, Sodium lauryl sulphate, Purified water, Methacrylic acid copolymer type C, Talc, Titanium dioxide, Triethyl citrate, Colloidal anhydrous silica, Sodium bicarbonate, Polyethyleneglycol sorbitan tristearate, Polydimethylsiloxane, Methylated silica, Methylcellulose, Polyvinyl alcohol, Polyethylene glycol, FD&C Yellow # 6 aluminium lake, FD&C Red # 40 aluminium lake, Lecithin, FD&C Blue # 1 aluminium lake.

650 mg Tablets: Microcrystalline cellulose, Guar gum, Corn starch, Hydrogenated vegetable oil type I, Sodium lauryl sulphate, Purified water, Methacrylic acid copolymer type C, Talc, Titanium dioxide, Triethyl citrate, Colloidal anhydrous silica, Sodium bicarbonate, Polyethyleneglycol sorbitan tristearate, Polydimethylsiloxane, Methylated silica, Methylcellulose, Polyvinyl alcohol, Polyethylene glycol, FD&C Yellow # 6 aluminium lake, Lecithin.

STORAGE AND STABILITY

Store at 15 - 30˚C. Protect from moisture.

INFORMATION FOR THE PATIENT

pms-ASA EC
Acetylsalicylic Acid Delayed-release Tablets USP

DESCRIPTION

WHAT pms-ASA EC CONTAINS

pms-ASA EC Tablets contain acetylsalicylic acid, also known as ASA.

WHAT pms-ASA EC DOES

pms-ASA EC Tablets have the following characteristics:

Action

pms-ASA EC Tablets contain ASA. Clinical practice has established the suitability of ASA in relieving pain associated with conditions such as minor body aches, muscle, back and joint pain.

Special, enteric coating to help prevent stomach upset

The special enteric coating of pms-ASA EC enables the tablet to pass, undissolved, through the acidic stomach and enter the upper portion of the small intestine, a less acidic environment. It is then that the tablet is dissolved, thus it is less likely to cause stomach irritation that is sometimes associated with plain or buffered ASA.

Onset of Action

Because pms-ASA EC Tablets are specially coated to reduce the risk of stomach upset, the ASA is not absorbed by the stomach and the onset of action will be somewhat delayed.

WHEN TO TAKE pms-ASA EC

pms-ASA EC is indicated for the relief of minor aches and pains, including the pain of inflammation associated with arthritis and rheumatism. pms-ASA EC may be used for backache, bursitis pain, knee pain, joint pain, muscle aches, lower back pain, tennis elbow. It is also useful in relieving pain and aches associated with colds.

HOW TO TAKE pms-ASA EC

ADULTS

The tablets must be swallowed whole, with a large glass of water (250 mL); do not crush or break up. It is hazardous to exceed the maximum recommended dose (650 mg per single dose or 4 g daily) unless advised by your physician. Consult your physician if your condition does not improve after 5 days of continued product use.

PRECAUTIONS

If you are taking other medication, carefully read the labels to ensure that they do not also contain acetylsalicylic acid which could result in an overdose. If in doubt, consult your physician or pharmacist.
If you expect to undergo surgery, including dental surgery within 5 to 7 days of taking ASA or pms-ASA EC Tablets, consult your physician or pharmacist.

Consult a physician before taking this drug during the last three months of pregnancy or when breast-feeding.

DO NOT ADMINISTER pms-ASA EC to children or teenagers who have chicken pox or flu symptoms before a physician or pharmacist is consulted about Reye's Syndrome, a rare and serious illness.

There is enough drug in each package to seriously harrn a child.
Keep this medicine out of the reach of children.

WHEN TO CONSULT YOUR PHYSICIAN OR PHARMACIST ABOUT pms-ASA EC

A physician or pharmacist should be consulted prior to taking this medication in case of:

- allergy to salicylates or asthma
- during pregnancy or when breast-feeding
- if you have stomach problems, peptic ulcer, severe liver disease or gout

  a history of blood coagulation defects, or when receiving anticoagulant drugs
- ASA is not recommended 5 to 7 days prior to surgery or in the presence of severe anemia
- intake of other medications containing salicylates or acetaminophen, anti-inflammatory drugs, anticonvulsants, anti-diabetic or gout medicine.

POSSIBLE SIDE EFFECTS

pms-ASA EC Tablets occasionally may produce some unwanted effects. A physician should be contacted if any of the following reactions develop during treatment:

- bleeding or irritation of stomach (nausea, vomiting, pain)
- any loss of hearing, including ringing or buzzing in the ears
- skin rashes, hives or itching
- breathing difficulties.

WHAT TO DO IN CASE OF OVERDOSE

IN CASE OF ACCIDENTAL OR SUSPECTED OVERDOSE, CONTACT A PHYSICIAN, A POISON CONTROL CENTRE, OR THE EMERGENCY DEPARTMENT OF A HOSPITAL IMMEDIATELY, EVEN IF THERE ARE NO SYMPTOMS.

The signs and symptoms of an overdose usually occur within a few hours after ingestion. They may include:
stomach upset, convulsions (seizures), hearing loss, mental confusion, ringing or buzzing in the ears, severe drowsiness or tiredness, severe excitement or nervousness and unusually fast or deep breathing, hallucinations or changes in behaviour (especially in children).

DESCRIPTION

Enteric-coated tablets printed in black with product name and potency declared in mg per tablet.

REGULAR STRENGTH EN pms-ASA EC	**SUPER EXTRA STRENGTH pms-ASA EC**
325 mg Tablets	650 mg Tablets
Usual Dosage 1-2 tablets every four hours	*Usual Dosage* 1 tablet every four hours
Maximum daily dosage (4000 mg a day) 12 tablets	Maximum daily dosage (4000 mg a day) 6 tablets
For low dose ASA therapy. For relief of mild aches and pains due to muscle and joint strain	For relief of moderate joint pain caused by arthritis and athletic injuries.

Product Monograph available to pharmacists and physicians upon request.

pms-ASA EC

Acetylsalicylic Acid Delayed-Release Tablets 325 mg USP
FOR LONG-TERM ASA PREVENTATIVE THERAPY

This leaflet gives you important information on pms-ASA EC and how to use it for Long-Term ASA Preventative Therapy. Please read carefully before using this medicine.

WHY DID MY DOCTOR RECOMMEND pms-ASA EC

- Different than dosing regimens for conditions such as arthritis, your doctor recommended a lower dose ASA regimen of pms-ASA EC for supervised adult long-term preventative therapy. Follow your doctor's instructions on how to take this medication. Contact your doctor if you have any questions about your therapy or your condition.

- pms-ASA EC has a special formulation of ASA (Acetylsalicylic Acid) recommended by your doctor for your condition.

HOW DOES THE SPECIALLY-FORMULATED pms-ASA EC

- The special enteric coating of pms-ASA EC enables the tablet to pass, undissolved, through the acidic stomach and enter the upper portion of the small intestine, a less acidic environment. It is then that the tablet is dissolved, thus it is less likely to cause stomach irritation that is sometimes associated with plain or buffered ASA.

HOW SHOULD I TAKE THIS MEDICATION

It is very important that you take this medicine as directed by your doctor. Do not take this medicine until you have seen your doctor.

Adult Dosage: 1 tablet (325 mg) daily or every second day, according to the individual needs of the patient as directed by a physician. Therapy to continue indefinitely under a doctor's supervision. The tablets must be swallowed whole, with a large glass of water (250 mL); do not crush or break up.

Follow your doctor's instructions on lifestyle changes, such as diet and exercise.

It is hazardous to exceed the maximum recommended dose unless advised by a physician.

ARE THERE SIDE EFFECTS WITH THIS MEDICINE

Like all medicines, ASA may occasionally produce some unwanted effects. A physician should be contacted if any of the following reactions develop during treatment:

- bleeding or irritation of stomach (nausea, vomiting, pain)
- any loss of hearing, including ringing or buzzing in the ears
- skin rashes, hives or itching a breathing difficulties.

WHAT ELSE SHOULD I KNOW BEFORE I TAKE THIS MEDICINE

Your doctor will have considered your specific condition before recommending a preventative therapy regimen of pms-ASA EC. Therefore, it is important to keep your doctor informed of all details regarding your health, lifestyle and medications.

If you forgot to tell your doctor about any of the following, call your doctor or pharmacist before taking this medicine:

- allergy to salicylates or asthma
- during pregnancy or when breast-feeding
- if you have stomach problems, peptic ulcer, severe liver disease or gout
- a history of blood coagulation defects, or when receiving anticoagulant drugs
- ASA is not recommended 5 to 7 days prior to surgery or in the presence of severe anemia
- intake of other medications containing salicylates or acetaminophen, anti-inflammatory drugs, anticonvulsants, anti-diabetic or gout medicine.

WHAT SHOULD I DO IN CASE OF OVERDOSE

In case of accidental or suspected overdose, contact a physician, a poison control centre, or the emergency department of a hospital immediately, even if there are no symptoms.

The signs and symptoms of an overdose usually occur within a few hours after ingestion. They may include:

stomach upset, convulsions (seizures), hearing loss, mental confusion, ringing or buzzing in the ears, severe drowsiness or tiredness, severe excitement or nervousness and unusually fast or dee) breathing, hallucinations or changes in behaviour (especially in children).

IMPORTANT PRECAUTIONS

If you are taking other medication, carefully read the labels to ensure that they do not also contain acetylsalicylic acid which could result in an overdose. If in doubt, consult your physician or pharmacist.
If you expect to undergo surgery, including dental surgery within 5 to 7 days of taking ASA or pms-ASA EC Coated Tablets, consult your physician or pharmacist.

Consult a physician before taking this drug during the last three months of pregnancy or when breast-feeding.

Regular daily use of alcohol while on ASA daily therapy may increase your risk of developing gastrointestinal bleeding.

DO NOT ADMINISTER pms-ASA EC to children or teenagers who have chicken pox or flu symptoms before a physician or pharmacist is consulted about Reye's Syndrome, a rare and serious illness.

- **CAUTION: There is enough drug in each package to seriously harm a child. Keep this medicine out of the reach of children.**

pms-ASA EC is available as a tablet.

Medicinal Ingredient: Acetylsalicylic Acid 325 mg and 650 mg.

Product Monograph available to physicians and pharmacists on request.

PHARMACOLOGY

The absorption of salicylates occurs predominantly by passive diffusion of undissociated drug molecules across gastrointestinal membranes (Schanker et al, 1958). ASA is rapidly hydrolyzed to salicylic acid. Salicylate is widely distributed throughout the body with highest concentrations found in the kidney, cortex, liver, heart, and lung. Brain concentrations are relatively low (Davidson et al, 1961). Salicylate metabolism differs in various species. Conjugation is relatively slow in men; however, it probably occurs in many tissues. The chief metabolic products in men are the conjugates with glycine (salicyluric acid) the ether or phenolic glueuronide (salicylic phenolic glucuronide), and the ester or acyl glucuronide (salicylic acyl glucuronide).

A small fraction is oxidized to gentisic and other hydroxybenzoic acids. Excretion of salicylates is almost entirely via the kidney. No salicylic compounds can be found in the urine or blood about 48 hours after the last dose (Milne, 1963), the excretion rate of free salicylate is highly variable and is dependent primarily on urinary pH; they are also influenced by glomerular filtration, proximal tubular secretion and urine flow rates. Urinary alkalinity increases the excretion of salicylate; small pH changes in alkaline urine may have a considerable effect, but pH changes in the acid range have little effect on the excretion rate. The excretion of salicylate conjugates is more affected by changes in glomerular filtration or proximal tubular secretion than by changes in urine flow or urine pH. However, urinary pH does affect the proportion excreted as metabolites. The mean free salicylate in human urine was found to be 61 % in studies using C14 labelled salicylate (Milne, 1963), in alkaline urine, up to 85%, whereas in acid urine, free salicylate may amount to only 10% of the ingested dose.

Thus, the amounts of metabolic products found in the urine have shown a wide range: salicyluric acid, 0 to 60% of the ingested dose (mean 8%); salicylic phenolic glucuronide, 12 to 30% (mean 22%); salicylic acyl glucuronide, 0 to 10% (mean 5%); and gentisic acid about 1%. The uricosuric action of salicylate has been confirmed repeatedly. However, at low dosage of salicylate, less than 2 g per day there is a paradoxical reversal of this action and urate is retained (Yu & Gutman, 1959). High doses, 5 to 8 g per day are required for consistent uricosuria. Salicylates exert inhibitory effect on at least 3 vital groups of cellular enzymes, those concerned with oxidative phosphorylation, the transaminases and the dehydrogenases, (Smith, 1963). Studies in vitro and in vivo have shown that salicylates depress the biosynthesis of mucopolysaccharide sulfates in representative connective tissues, cartilage, heart valves and cornea (Whitehouse, 1963).

Salicylates may reduce the blood sugar of both maturity onset and juvenile type diabetics, the fasting blood sugar being more affected than postprandial levels (Stowers, 1963).

At concentrations encountered clinically, from 50 to 90% of the salicylate is bound to plasma proteins, especially albumin. Hypoalbuminemia, as may occur in rheumatoid arthritis, is associated with a proportionately higher level of free salicylate in the plasma. Salicylate stimulates respiration directly and indirectly. Full therapeutic doses of salicylates increase oxygen consumption and carbon dioxide production in experimental animals and men.

Established actions of ASA include suppression of antibody production, interference with antigen-antibody aggregation, inhibition of antigen-induced histamine release in vitro, and stabilization of capillary permeability in the presence of either immunological or non-immunological insults.

ASA inhibits platelet aggregation by irreversibly acetylating platelet cyclooxygenase thereby preventing the formation of thromboxane A2 production. Maximal inhibition of thromboxane A2 production and platelet aggregation can be obtained with ASA doses of 300 mg (Jakubowski, 1985). Enteric-coated ASA formulations are also effective at doses of 325 mg (Cerietti, 1987). Recovery of platelet cyclooxygenase activity after a single dose of enteric coated ASA is delayed 48-72 hours (Jakubowski, 1985). Suppression of platelet thromboxane A2 production has also been shown to persist for at least 48 hours after seven doses of enteric coated ASA 325 mg administered on alternate days (Stampfer, 1986). Platelet aggregation is believed to be an important element in unstable coronary artery disease. Several clinical trials have shown that ASA administered in doses of 325-1500 mg/day reduces the incidence of myocardial infarction and death in patients with unstable angina (Cairns, 1985; Lewis, 1983) or previous myocardial infarction (Bredin, 1980; Elwood, 1974).

TOXICOLOGY

ACUTE TOXICITY

LD_{50}

(Abdernalden, 1935 - Khera, K.S. 1976 - Boyd, E.M. 1959 - Brossi, A. et al, 1965)

SPECIES	ROUTE	LD50 (mg/kg)
Mice	P.O.	700-1100
Rats	P.O.	800-2000
Rabbits	P.O.	1000-1800
Dogs	I.V.	681
Mice	I.P.	420

On the basis of his own studies and analysis of the work of other investigators, Boyd concluded that the acute oral LD_{50} of ASA in all species studies, including man, is on the order of 1 to 2 g/kg.

Symptoms produced in rats by doses in this range were inactivity, lack of alertness or curiosity, cataleptic tenseness, anorexia, diarrhea, nosebleed, hyperreflexia, and convulsive twitching. Deaths occurring within one day were due to tonic-clonic convulsions and respiratory failure.

The respiratory changes induced by salicylates are partly due to their metabolic influence on oxygen consumption and C02 production, and are also brought about through their effects on the central nervous system. Respiratory failure may be a cause of death in the rat, as in man.

Deaths on the second and third days were due to cardiovascular shock. Autopsy revealed gastro-enteritis, hepatitis, nephritis, pulmonary edema, and lesser changes in numerous tissues. Toxic symptoms in other species are similar.

The lowest lethal dose (LDL) of ASA reported in the literature is 104 mg/kg for a child.

CHRONIC TOXICITY

ASA in concentrations of 130, 625, or 1270 mg/kg/day (2 to 20 times the maximum tolerated clinical dose of 4 g daily) was administered in the diet of mice for prolonged periods. All dosages had a deleterious effect on mean survival time, number of young bom, and number of young raised to weaning age, with the largest dose showing the strongest effects. (Wright, H.N., 1967)

Studies have demonstrated growth retardation in immature rats after chronic oral administration of sodium salicylate or sodium acetylsalicylate (Limbeck, G.A. et al, 1966) and nephrotoxic effects in adult rats after intraperitoneal administration of 400 mg/kg or more of sodium salicylate. (Robinson, M.J. et al, 1967)

The damaging effect of ASA on the gastric mucosa has been studied by many investigators, but the mechanism of action is still unknown.

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