

PRODUCT MONOGRAPH

CHEWABLE DAILY LOW DOSE ASA
(Acetylsalicylic acid chewable tablets, USP)
81 mg

Analgesic, anti-inflammatory, antipyretic and
platelet aggregation inhibitor

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THERAPEUTIC OR PHARMACOLOGICAL CLASSIFICATION

Analgesic, anti-inflammatory, anti-pyretic and platelet aggregation inhibitor.

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.

The antipyretic activity of ASA is due to its ability to interfere with the production of prostaglandin E₁ in the brain. Prostaglandin E₁ is one of the most powerful pyretic agents known.

The inhibition of platelet aggregation by ASA is due to its ability to interfere with the production of thromboxane A₂ within the platelet. Thromboxane A₂ is largely responsible for the aggregating properties of platelets.

INDICATIONS AND CLINICAL USE

Acetylsalicylic acid (ASA) is indicated for the relief of pain, fever and inflammation of a variety of conditions such as influenza, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, fractures, myositis, neuralgia, synovitis, arthritis, bursitis, burns, injuries, following surgical and dental procedures.

CHEWABLE DAILY LOW DOSE ASA 81 mg are also indicated for the following uses, based on its platelet aggregation inhibitory properties:

- 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 transient ischemic attacks (TIA) and for secondary prevention of atherothrombotic cerebral infarction;

- For prophylaxis of venous thromboembolism after total hip replacement;

- For reduction of adhesive properties of platelets in patients following carotid endarterectomy to prevent recurrence of TIA and in hemodialysis patients with a silicone rubber arteriovenous cannula.

In addition, CHEWABLE DAILY LOW DOSE ASA 81 mg is also indicated for the following uses, based on its platelet aggregation inhibitory properties:

- For reducing the risk of vascular mortality in patients with a suspected acute myocardial infarction.

- For reducing the risk of a **first** non-fatal myocardial infarction in individuals deemed to be at sufficient risk of such an event by their physician. There is no evidence for a reduction in the risk of **first** fatal myocardial infarction. ASA does not reduce the risk of

either cardiovascular mortality or **first** strokes, fatal or non-fatal. The decrease in the risk of **first** non-fatal myocardial infarction must be assessed against a much smaller but not insignificant increase in the risk of haemorrhagic stroke as well as gastrointestinal bleeding.

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.

A possible association between Reye's syndrome and the use of salicylates has been suggested but not established. Reye's syndrome has also occurred in many patients not exposed to salicylates. However, caution is advised when prescribing salicylate-containing medications for children and teenagers with influenza or chickenpox.

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 overdose these may include rapid and deep breathing, nausea, vomiting, vertigo, tinnitus, flushing, sweating, thirst, and 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 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 overdose 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

Analgesic and antipyretic:

Adults: 1-2 tablets (325 mg to 650 mg) orally every 4 hours.

Children under 12: 10 to 15 mg/kg every 6 hours, not to exceed a total daily dose of 2.4 g.

Anti-inflammatory:

Adults: 3 tablets (975 mg) 4 to 6 times a day, up to 30 tablets daily, may be required for optimal anti-inflammatory effect. A blood level between 15 and 30 mg per 100 mL is in the desirable therapeutic range.

Children: 60 to 125 mg/kg daily in 4 to 6 divided doses.

Platelet aggregation inhibitor:

- For reducing the risk of morbidity and death in patients with unstable angina and in those with previous myocardial infarction: 80 - 325 mg daily according to the individual needs of the patient, as determined by the physician. **CHEWABLE DAILY LOW DOSE ASA 81 mg (Acetylsalicylic acid chewable tablets) is specifically indicated for these uses.**

- For reducing the risk of transient ischemic attacks (TIA) and for secondary prevention of atherothrombotic cerebral infarction: 80 - 325 mg daily according to the individual needs of the patient, as determined by the physician. **CHEWABLE DAILY LOW DOSE ASA 81 mg (Acetylsalicylic acid chewable tablets) is specifically indicated for these uses.**

- For prophylaxis of venous thromboembolism after total hip replacement: 650 mg twice a day (1,300 mg daily), started 1 day before surgery and continued for 14 days. **CHEWABLE DAILY LOW DOSE ASA 81 mg (Acetylsalicylic acid chewable tablets) is specifically indicated for these uses.**

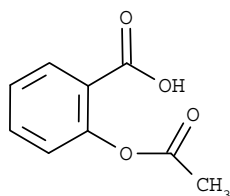
PHARMACEUTICAL INFORMATION

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

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

CHEWABLE DAILY LOW DOSE ASA:

Each chewable tablet contains 81 mg acetylsalicylic acid as active ingredient.

Non-medicinal ingredients: DC Yellow #10, FDC Red #40, mannitol, orange flavor, pregelatinized starch, sodium saccharin, stearic acid.

AVAILABILITY OF DOSAGE FORM

CHEWABLE DAILY LOW DOSE ASA:

Each chewable, salmon coloured, round, biconvex tablet, embossed "81" contains 81 mg acetylsalicylic acid. In packages of 30, 120, 150 and 180 tablets.

STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature (15°-30°C).

PATIENT INFORMATION TO BE DISTRIBUTED ONLY BY PHYSICIANS/PHARMACISTS

CHEWABLE DAILY LOW DOSE ASA 81 mg

This section provides you with information about **CHEWABLE DAILY LOW DOSE ASA 81 mg** acetylsalicylic acid (chewable) tablets and how to take this medication. *Please read carefully before you take this medication.*

Your physician has recommended **CHEWABLE DAILY LOW DOSE ASA 81 mg** for supervised adult long-term preventative therapy.

Follow your physician's instructions concerning the use of **CHEWABLE DAILY LOW DOSE ASA 81 mg** as well as any lifestyle changes, e.g. diet and/or exercise that he/she may have recommended. Always contact your physician if you experience any difficulties while taking this product.

CHEWABLE DAILY LOW DOSE ASA 81 mg contains acetylsalicylic acid, commonly referred to as ASA, as its active ingredient. Plain (uncoated) ASA, particularly when taken regularly, may cause stomach upset in some people. The special enteric coating of **CHEWABLE DAILY LOW DOSE ASA 81 mg** tablets allows them to pass intact through the stomach and on into the intestine before they dissolve which may reduce the risk of stomach upset.

Your physician has specifically recommended **CHEWABLE DAILY LOW DOSE ASA 81 mg** because it contains a special, low-dose, enteric-coated, formulation of ASA. Other medications such as acetaminophen or ibuprofen that are meant to relieve pain do not have the same preventative action as **CHEWABLE DAILY LOW DOSE ASA 81 mg** which has been specifically formulated for your condition.

DIRECTIONS FOR USE

It is very important that you take this medication as directed by your physician. If you have not seen a physician, do not take this medication until you have done so.

Dosage:

1 to 4 tablets daily of **CHEWABLE DAILY LOW DOSE ASA 81 mg** depending on your doctor's instructions. Your doctor may tell you to take or with other medications. He/she may also advise you to make certain lifestyle changes, (e.g. diet, exercise, smoking cessation), to safeguard your health. You should take this medication at the same time every day to help you to remember to take it. For maximum effectiveness, it is very important to take **CHEWABLE**

DAILY LOW DOSE ASA 81 mg every day, as directed by your physician. Do not take more tablets than your physician recommends.

CHEWABLE DAILY LOW DOSE ASA 81 mg (Acetylsalicylic Acid Chewable) Tablets are chewable and therefore must be chewed well and swallowed.

ANSWERS TO COMMONLY ASKED QUESTIONS

WHY WAS CHEWABLE DAILY LOW DOSE ASA 81 mg RECOMMENDED BY MY DOCTOR?

FOR PREVENTION OF A SECOND HEART ATTACK OR STROKE (DAILY THERAPY)

It can be used to prevent a second stroke or heart attack. If you have experienced either a stroke or a heart attack you may be at risk for a second one. There are certain risk factors that can place you at an increased risk:

- Overweight
- Smoking
- Inactive (sedentary) lifestyle
- Stress
- High blood cholesterol
- High blood pressure

These can be discussed with your physician in order to complement the effectiveness of **CHEWABLE DAILY LOW DOSE ASA 81 mg.**

Your doctor may recommend changes in diet, exercise and lifestyle for your benefit in avoiding a second heart attack or stroke.

If you experience any difficulties with your treatment always discuss with your doctor or pharmacist.

USE DURING A HEART ATTACK

If you think you are having a heart attack, you should immediately chew 2 **CHEWABLE DAILY LOW DOSE ASA 81 mg** tablets and call an ambulance. It is important to chew or crush the product, to ensure this medicine quickly works. Then get to a hospital immediately for medical attention. Taking **CHEWABLE DAILY LOW DOSE ASA 81 mg** at the first signs and symptoms can reduce your risk of dying from the heart attack.

The signs and symptoms of a heart attack include:

1. uncomfortable pressure, fullness, squeezing or pain in the center of the chest that lasts more than a few minutes, or goes away quickly and comes back,
2. pain that spreads to the shoulders, neck or arms,
3. chest discomfort with lightheadedness, fainting, sweating, nausea or shortness of breath.

At the hospital, the doctor will then recommend appropriate therapy

WHAT IF I FORGET TO TAKE MY MEDICATION?

If you forget to take your medication at the usual time, take it when you remember. Do not take extra medication to compensate for a missed dosage unless instructed by your physician.

WILL I EXPERIENCE ANY SIDE EFFECTS WITH THIS MEDICINE?

Like any medication, ASA may occasionally produce unwanted side effects. You should call your physician if you experience any of the following: nausea, vomiting, bleeding or stomach irritation, dizziness, weakness, fainting spells, any loss of hearing, including ringing or buzzing in the ears or pain; skin rashes, hives or itching and breathing difficulties. Regular use of alcohol while on ASA daily therapy may increase your risk of developing gastrointestinal bleeding.

WHAT ELSE SHOULD I KNOW BEFORE TAKING THIS MEDICINE?

Your doctor will ask you many questions about your health, lifestyle, and medications before recommending **CHEWABLE DAILY LOW DOSE ASA 81 mg**.

This is why it is very important that you tell your doctor all such information. If you have forgotten to tell your doctor about any of the following, call your doctor or pharmacist before you take this medicine.

- Allergy to salicylates
- Asthma
- Stomach problems
- Peptic ulcer
- Severe liver disease
- Severe anemia
- Are pregnant or breast-feeding
- Will be having surgery in five to seven days
- Are taking other medications containing salicylates or acetaminophen
- Are taking anti-inflammatory drugs, anticonvulsants, anti-diabetics or gout medication
- Are taking or planning to take this medication while consuming alcohol
- History of blood clotting defects or receiving blood thinners

CAUTION

This product is not recommended for children or teenagers. This package contains enough drug to seriously harm a child. Keep out of children's reach. Do not administer to children and teenagers for chicken pox or flu symptoms before a doctor is consulted. Reye's Syndrome, which can occur in children or teenagers, is a rare but serious illness reported to be associated with ASA.

It is especially important not to use this medication during the last 3 months of pregnancy unless specifically directed to do so by your physician because it may cause problems in the unborn child or complications during delivery.

Call your doctor before taking this drug when nursing.

In case of accidental overdose call a doctor or hospital immediately, even if there are no symptoms.

Product Monograph is available to health professionals upon request.

For further information or questions about this product, contact Pharmascience Inc., Montreal, Canada at their Medical Information Hotline between 8:30am and 4:30pm, Eastern Standard Time, Monday to Friday. Call toll-free at 1-888-550-6060.

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.

Antipyresis:

Interference with the synthesis and release of prostaglandins is also involved in ASA's antipyretic activity. ASA effects a significant reduction in elevated body temperature, but has little effect on normal body temperature. This latter is maintained by a delicate balance between heat production and heat loss, with the hypothalamus regulating the set point at which body temperature is maintained. Fever is induced by synthesis and release of prostaglandins in this

temperature-regulating area and ASA acts by interfering with this process. Heat production is not inhibited but dissipation of heat is augmented by increased peripheral blood flow and by sweating.

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.

Effects on platelets: relation to hemostasis and thrombosis.

Platelets play an important role in normal hemostasis and clinical pathologic and experimental evidence indicates that their aggregation may play an equally important role in the evolution of a variety of disease states including cerebrovascular disease, ischemic heart disease and myocardial infarction. CHEWABLE DAILY LOW DOSE ASA 81mg inhibits platelet aggregation by irreversibly acetylating platelet cyclo-oxygenase, thereby blocking the production of prostaglandin endoperoxides PGG₂ and PGH₂ which are precursors of the major platelet-aggregating material, thromboxane A₂, which is also a powerful vasoconstrictor. However, CHEWABLE DAILY LOW DOSE ASA 81mg does not prevent the adherence of platelets to damaged vessel walls or the release of granule contents from these adherent platelets. As the anuclear platelets are unable to synthesize new enzyme molecules to replace those that have been

inactivated, inhibition of platelet aggregation by CHEWABLE DAILY LOW DOSE ASA 81mg thus persist for the life of the platelets.

Daily administration of 20 to 40 mg of ASA to healthy volunteers reduced platelet thromboxane production but inhibited platelet aggregation only partially. When administered to patients recovering from myocardial infarction, 50 mg ASA daily had the same effects on thromboxane production, platelet aggregation and bleeding times as 324 mg daily. Other studies show that ASA doses of 40 to 325 mg daily suppressed thromboxane production by at least 80 %, but 80 mg ASA daily was the lowest dose required for maximum cumulative thrombocyte function inhibition. The protective effect of ASA against experimentally induced thrombosis or atherosclerosis has been demonstrated in several animal models.

Besides inhibiting the biosynthesis of thromboxane A₂ by platelets, ASA also interferes with the production of prostacyclin (PGI₂) by vascular endothelial cells, the above-mentioned prostaglandin endoperoxides being common precursors of both thromboxane A₂ and prostacyclin. This latter compound is one of the most powerfully acting platelet deaggregators and vasodilators and thus it would appear that the interference with the hemostatic processes by ASA depends on the thromboxane-prostacyclin balance. In fact, it has been suggested that under some conditions, high doses of ASA may be thrombogenic. However, in contrast to platelets, the vascular endothelial cells are able to regenerate cyclo-oxygenase in a relatively short time and therefore therapeutic doses of ASA are likely to produce a lesser inhibition of the vascular prostacyclin system than of the platelet thromboxane-forming mechanism. In fact, there is no clinical evidence to indicate that high doses of ASA would result in an increased risk of thromboembolism. Indeed, quite the contrary was observed and , in a controlled study, paradoxical shortening of the bleeding time was not observed at a daily ASA dose 3.6 g. Lower dosages of ASA make selective blocking of the TxA₂-synthesis without a simultaneous blocking of PGI₂-production possible.

The use of ASA in patients with a suspected acute myocardial infarction was investigated in a large multicenter trial involving over 17,000 patients. Treatment with ASA resulted in a 23% reduction in the risk of vascular mortality versus placebo at 5 weeks. This use translates to a reduction of 24 deaths and 14 non-vascular events per 1000 patients treated.

The effect of time to therapy revealed that patients treated with ASA “early” (0 to 4 hours) versus “late” (5 to 24 hours) after symptom onset experienced reductions in the odds of vascular death of 25% versus 21%, versus placebo at 5 weeks. ‘Early’ treatment with ASA resulted in the saving of 4 additional lives per 1000 patients versus ‘late’ treatment.

Long term follow-up (up to 10 years) of patients in this study established that the early survival advantage to ASA persisted long term, and that this prolonged benefit was additive to that of fibrinolytic therapy.

The use of ASA for secondary prevention of thrombotic events is supported by a comprehensive overview of a number of clinical trials involving patients who already had some type of vascular disease (myocardial infarction, unstable angina, stroke or transient cerebral ischemia). Overall, these studies point to a 26-28% reduction of the combined endpoints of MI, stroke, or vascular deaths by treatment with ASA alone at doses of 75 to 325 mg daily. Studies which directly compared low doses with higher doses (30-1200 mg/day), indicated that the incidence of gastrointestinal adverse effects were significantly less common with the lower doses.

Recent discussions have focused on the efficacy of ASA for the primary prevention of myocardial infarction and stroke. Two large scale randomized trials, aimed at evaluating prophylactic use of ASA, were conducted among apparently healthy male physicians (22,000 in the United States and 5,000 in the United Kingdom respectively and their results have been published. In the summary overview of the combined results presented by the principal investigators, the authors state that:

“.....Taken together, these two primary-prevention studies demonstrate a significant ($P<0.0001$) reduction in nonfatal myocardial infarction of about one third.”

On the other hand, the same two studies have not indicated any reduction in overall vascular mortality and also suggested a slight increase in the risk of non-fatal disabling stroke. Current controversy exists about the applicability of these findings, obtained in a selected population, to

the general public. As well, the optimum dosage regimen still remains an open question in this regard. Thus, the use of ASA for primary prevention should remain, in the words of the principal investigators:

“A matter of judgment in which the physician considers the cardiovascular risk profile of the patient and balances the known hazards of aspirin...against the clearly established reduction in the incidence of a first myocardial infarction.”

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 LD₅₀ 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 LD₅₀ 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, piloerection, 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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