PRODUCT MONOGRAPH

ASA
(Acetylsalicylic acid delayed-release tablets, USP)
81 mg

Platelet aggregation inhibitor

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PRODUCT MONOGRAPH

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81 mg

THERAPEUTIC OR PHARMACOLOGICAL CLASSIFICATION

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 E_1 in the brain. Prostaglandin E_1 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 A_2 within the platelet. Thromboxane A_2 is largely responsible for the aggregating properties of platelets.

INDICATIONS AND CLINICAL USE

Acetylsalicylic acid (ASA) is 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;

In addition, ASA 81 mg are 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 significant increase in the risk of haemorrhagic stroke as well as gastrointestinal bleeding.

CONTRAINDICATIONS

Use of ASA 81 mg is contraindicated in patients:

- who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see COMPOSITION and AVAILABILITY OF DOSAGE FORMS sections of the product monograph.
- with a history of asthma induced by the administration of salicylates or substances with a similar action, notably non-steroidal anti-inflammatory drugs
- also taking methotrexate at doses of 15 mg/week or more
- during their last trimester of pregnancy
- with any Hemorrhagic diathesis
- with an Active peptic ulcer.

WARNINGS AND PRECAUTIONS

General

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.

Salicylates should be administered cautiously to patients with:

- Hypersensitivity to anti-inflammatory or antirheumatic drugs or other allergens
- impaired renal function or hepatic function
- a history of chronic or recurrent gastrointestinal ulcerations and bleeds
- a history of bleeding tendencies, significant anemia and/or hypothrombinemia

Hypersensitivity

Acetylsalicylic acid (ASA) may precipitate bronchospasm and induce asthma attacks or other hypersensitivity reactions. Risk factors are present bronchial asthma, hay fever, nasal polyps, or chronic respiratory disease. This applies also for patients showing allergic reactions (e.g. cutaneous reactions, itching, urticaria) to other substances.

Hematologic

Due to effect on platelet aggregation, ASA may be associated with an increased risk of bleeding. Caution is necessary when salicylates and anticoagulants are prescribed concurrently, as salicylates can depress the concentration of prothrombin in the plasma.

Peri-Operative Considerations

Due to its inhibitory effect on platelet aggregation ASA may lead to an increased bleeding tendency during and after surgical operations (including minor surgeries, e.g. dental extractions).

Special Populations

Pregnant Women:

Use of salicylates in the first 3 months of pregnancy has been associated in several epidemiological studies with an elevated risk of malformations (cleft palate, heart malformations). After normal therapeutic doses this risk seems to be low: a prospective study with exposure of about 32,000 mother-child pairs has not yielded any association with the risk of malformations.

Salicylates should be taken during pregnancy only after strict risk benefit evaluation.

In the last 3 months of pregnancy, administration of salicylates in high doses (>300mg/day) can lead to prolongation of the gestation period, premature closure of the arterial duct and inhibition of uterine contractions. An increased hemorrhagic tendency has been observed in both mother and child.

Administration of ASA in high doses (> 300 mg/d) shortly before birth, can lead to intracranial hemorrhages, particularly in premature babies.

Nursing Women:

Acetylsalicylic acid (ASA) and its metabolites pass into breast milk in small quantities. Since no adverse effects on the infant have been observed after occasional use, interruption of breast-

feeding is usually unnecessary. However, on regular use or on intake of high doses, breast feeding should be discontinued early.

Pediatrics:

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. Acetylsalicylic acid (ASA) should not be used in children and teenagers for viral infections with or without fever without consulting a physician. In certain viral illnesses, especially influenza A, influenza B and varicella, there is a risk of Reye's syndrome, a very rare but possibly life-threatening illness requiring immediate medical action. The risk may be increased when ASA is given concomitantly; however, no causal relationship has been proven. Should persistent vomiting occur with such diseases; this may be a sign of Reye's syndrome.

Low Uric Acid Excretion:

At low doses, ASA reduces excretion of uric acid. This can trigger gout in patients who already tend to have low uric acid excretion.

Monitoring and Laboratory Tests:

Salicylates can produce changes in thyroid function tests.

Isolated cases of liver function disturbances (transaminases increase) have been described.

ADVERSE REACTIONS

Many adverse reactions due to ASA ingestion are dose-related. The following is a list of adverse reactions that have been reported in the literature and from both clinical and post-marketing experience.

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

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.

DRUG INTERACTIONS

Overview

Acetylsalicylic acid (ASA) should be used with caution with other products that have anticoagulation or antiplatelet effects, as these effects may be potentiated. Drugs that bind to protein binding sites should also be used cautiously since ASA may displace drugs from their protein, binding site.

Methotrexate, used at 15mg/week or less: Salicylates may retard the elimination of methotrexate by decreasing renal clearance of methotrexate, displacing methotrexate from protein binding sites, and thereby increasing its hematological toxicity.

Anti-coagulants, e.g. warfarin, heparin: Caution is necessary when salicylates and anticoagulants are prescribed concurrently, as salicylates can depress the concentration of prothrombin in the plasma.

Oral hypoglycemics, e.g. insulin, sulfonylureas: Large doses of salicylates have a hypoglycemic action and may enhance the effect of oral hypoglycemic agents. Diabetics receiving concurrent salicylate and hypoglycemic therapy should be monitored closely; reduction of the sulfonylurea hypoglycemic drug dosage may be necessary.

Diuretics: Sodium excretion produced by spironolactone may be decreased by salicylate

administration.

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

Valproic Acid: 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.

Glucocorticoids (systemic), except hydrocortisone used as replacement therapy in Addison's disease: Decreased blood salicylate levels during corticosteroid treatment and risk of salicylate overdose after this treatment is stopped via increased elimination of salicylates by corticosteroids.

Angiotensin Converting Enzyme (ACE) Inhibitors: The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by the concomitant administration of ASA due to its indirect effect on the rennin-angiotensin conversion pathway. The potential interaction may be related to the dose of ASA (3g/day or more).

Digoxin: Plasma concentrations of digoxin are increased due to a decrease in renal excretion.

ASA and other NSAIDs:

The use of other non-steroidal anti-inflammatory drugs with salicylates at high doses (≥3g/day) may increase the risk of ulcers and gastrointestinal bleeding due to a synergistic effect.

Ibuprofen: Ibuprofen may interfere with the cardioprotective effects and platelet aggregation inhibitory properties of ASA. Patients should talk to their doctor if they are on an ASA regimen and take ibuprofen for pain. Studies have shown that single doses and multiple doses of ibuprofen may interfere with the anti-platelet effects of low dose ASA.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herb have not been established.

Drug-Laboratory Interactions

Salicylates can produce changes in thyroid function tests.

Drug-Lifestyle Interactions

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

DOSAGE AND ADMINISTRATION

Platelet aggregation inhibitor:

- For suspected acute myocardial infarction: An initial dose of at least 160 -162.5 mg crushed to ensure rapid absorption as soon as a myocardial infarction is suspected. The same dose should be given as maintenance over the next 30 days. After 30 days, consider further therapy based on dosage and administration for prevention of recurrent MI (see Prior Myocardial Infarction).

- For the prevention of a first non-fatal myocardial infarction: 80 - 325 mg daily according to the individual needs of the patient, as determined by the physician.

- 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.

- 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.

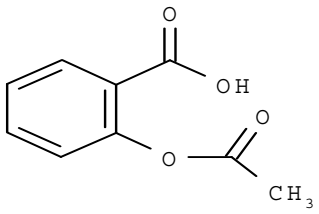
PHARMACEUTICAL INFORMATION

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

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

ASA: Each enteric-coated tablet contains 81 mg acetylsalicylic acid as active ingredient. Non-medicinal ingredients: Colloidal silicon dioxide, FD & C Blue #1, hydroxypropyl methylcellulose, lactose, methacrylic acid copolymer type C, methylated silica, methylcellulose, polydimethylsiloxane, polyethylene glycol, pregelatinized starch, siliconemulsion, sodium lauryl sulfate, sorbitan tristearate, stearic acid, talc, titanium dioxide, triethyl citrate.

AVAILABILITY OF DOSAGE FORM

ASA Each round, blue coated tablet contains 81 mg acetylsalicylic acid. In packages of 24, 30, 100, 120, 150, 180, 225, 250, 255 and 1000 tablets.

STABILITY AND STORAGE RECOMMENDATIONS

Store between 15°C and 30°C.

PATIENT INFORMATION TO BE DISTRIBUTED ONLY BY PHYSICIANS/PHARMACISTS

ASA

81 mg

(Acetylsalicylic Acid Delayed Release Tablets USP)

This leaflet is a summary and will not tell you everything about **ASA** 81 mg. Contact your doctor or pharmacist if you have any questions about the drug.

This section provides you with information about **ASA** 81 mg acetylsalicylic acid (enteric coated) tablets and how to take this medication. ***Please read carefully before you take this medication.***

Your physician has recommended **ASA** 81 mg for doctor-supervised adult long-term preventative therapy.

Follow your physician's instructions concerning the use of **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.

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 **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 **ASA** 81 mg because it contains a special, low-dose, formulation of ASA. Other medications such as acetaminophen or ibuprofen that are

meant to relieve pain do not have the same preventative action as **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 **ASA** 81 mg, depending on your doctor's instructions. 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 **ASA** 81 mg every day, as directed by your physician. Do not take more tablets than your physician recommends.

ASA 81 mg tablets must be swallowed whole for the medication to work properly. ASA 81 mg tablets have a special enteric coating designed to help prevent stomach upset. To benefit from this protection, the tablets should not be crushed or broken unless in the case of a heart attack.

NON-MEDICINAL INGREDIENTS

ASA 81 mg

Colloidal silicon dioxide, FD & C Blue #1, hydroxypropyl methylcellulose, lactose, methacrylic acid copolymer type C, methylated silica, methylcellulose, polydimethylsiloxane, polyethylene glycol, pregelatinized starch, silicon emulsion, sodium lauryl sulfate, sorbitan tristearate, stearic acid, talc, titanium dioxide, triethyl citrate.

ANSWERS TO COMMONLY ASKED QUESTIONS

WHY WAS ASA 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	-Stress
-Smoking	-High blood cholesterol
-Inactive (sedentary) lifestyle	-High blood pressure

These can be discussed with your physician in order to complement the effectiveness of 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, call an ambulance immediately, and crush (ASA 81 mg) and ingest 2 tablets. It is important to crush the product, to ensure this medicine works quickly. Then get to a hospital immediately for medical attention. Taking ASA 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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medication, ASA may occasionally produce unwanted side effects. You should call your doctor if you experience any of the following: nausea, vomiting, stomach irritation, ringing or buzzing in the ears or pain, or if you notice that you are bruising more easily than you were before starting a daily dose of ASA.

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

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Stop use and call your doctor if you experience an allergic reaction (skin rash, hives, itching or breathing difficulties); stomach bleeding, loss of hearing or bleeding.

WHEN IT SHOULD NOT BE USED

ASA should not be used if you:

- Are allergic to ASA or any ingredient within the formulation.
- Have an active stomach ulcer

- Have a history of asthma induced by salicylates or other anti-inflammatory drugs
- Are using methotrexate at doses of 15mg/week or more
- Are in the last trimester of pregnancy
- Are prone to 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 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/kidney 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

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Ibuprofen may interfere with the protective benefits of ASA. Talk to your doctor if you are on an ASA regimen and taking ibuprofen for pain.

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.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

HOW TO STORE IT

Keep out of reach of children

Store between 15°C and 30°C.

REPORTING SUSPECTED SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- **Online at MedEffect;**
- **By calling 1-866-234-2345 (toll-free);**
- **By completing a Consumer Side Effect Reporting Form and sending it by:**
  - **Fax to 1-866-678-6789 (toll-free), or**
  - **Mail to: Canada Vigilance Program**
    Health Canada

Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

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 8:30 am and 4:30 pm, 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.

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. ASA inhibits platelet aggregation by irreversibly acetylating platelet cyclo-oxygenase, thereby blocking the production of prostaglandin

endoperoxides PGG_2 and PGH_2 which are precursors of the major platelet-aggregating material, thromboxane A_2, which is also a powerful vasoconstrictor. However, ASA 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 ASA 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 A_2 by platelets, ASA also interferes with the production of prostacyclin (PGI_2) by vascular endothelial cells, the above-mentioned prostaglandin endoperoxides being common precursors of both thromboxane A_2 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 TxA_2-synthesis without a simultaneous blocking of PGI_2-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 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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