



# Aspirin-Uses, Adrs,

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# Therapeutic uses

- ▶ The analgesic–antipyretic dose of aspirin for adults is 324-1000 mg orally every 4-6 hours.
- ▶ The anti-inflammatory doses of aspirin recommended for arthritis, spondyloarthropathies, and systemic lupus erythematosus (SLE) range from 3-4 g/day in divided doses.
- ▶ The maximum recommended daily dose of aspirin for adults and children >12 years or older is 4 g.

# Therapeutic uses.....

- ▶ The keratolytic action of free salicylic acid is employed for the local treatment of warts, corns, fungal infections, and certain types of eczematous dermatitis. After treatment with salicylic acid, tissue cells swell, soften, and desquamate.
- ▶ Methyl salicylate (oil of wintergreen) is a common ingredient of ointments and deep-heating liniments used in the management of musculoskeletal pain; it is also available in herbal medicines and as a flavoring agent.

# Therapeutic uses.....

- ▶ Mesalamine (5-aminosalicylic acid) is a salicylate that is used for its local effects in the treatment of inflammatory bowel disease.
- ▶ Low doses of aspirin ( $\leq 100$  mg daily) are used widely for their cardio-protective effects.
- ▶ Aspirin is used widely for the prophylaxis of thromboembolic disease, especially in the coronary and cerebral circulation, and is coupled frequently with oral anticoagulants in patients with bio-prosthetic or mechanical heart valves.

# Therapeutic uses.....

- ▶ Irreversible inhibition of platelet function is the mechanism underlying the cardio-protective effect of aspirin; however, preoperative aspirin often is recommended prior to carotid artery stenting, carotid end arterectomy, and arterial bypass.
- ▶ Salicylates are contraindicated for fever associated with viral infection in children “Reye’s Syndrome”; for non-viral etiologies.

# Adverse drug reaction

## ▶ **Respiration:**

- ▶ Salicylates increase O<sub>2</sub> consumption and CO<sub>2</sub> production (especially in skeletal muscle) at anti-inflammatory doses.
- ▶ These effects are a result of uncoupling oxidative phosphorylation.
- ▶ The increased production of CO<sub>2</sub> stimulates respiration (mainly by an increase in depth of respiration with only a slight increase in rate).

# ADRs.....

- ▶ **Acid–Base and Electrolyte Balance and Renal Effects:**
- ▶ Therapeutic doses of salicylate produce definite changes in the acid–base balance and electrolyte pattern.
- ▶ Respiratory alkalosis is achieved by increased renal excretion of bicarbonate, which is accompanied by increased  $\text{Na}^+$  and  $\text{K}^+$  excretion; plasma bicarbonate is thus lowered, and blood pH returns toward normal. This is the stage of compensatory renal acidosis.

# ADRS.....

## ▶ **Cardiovascular Effects:**

- ▶ At high therapeutic doses ( $\geq 3\text{g}$  daily), as might be given for acute rheumatic fever, salt and water retention can lead to an increase ( $\leq 20\%$ ) in circulating plasma volume and decreased hematocrit (through a dilutional effect).
- ▶ There is a tendency for the peripheral vessels to dilate because of a direct effect on vascular smooth muscle. That result in increased in Cardiac output and work.



# ADRS.....

- ▶ **GIT effects:**
- ▶ The ingestion of salicylates may result in epigastric distress, nausea, and vomiting.
- ▶ Salicylates also may cause gastric ulceration, exacerbation of peptic ulcer symptoms (heartburn, dyspepsia), GI hemorrhage, and erosive gastritis. These effects occur primarily with acetylated salicylates (i.e., aspirin).
- ▶ Because non-acetylated salicylates lack the ability to acetylate COX and thereby inhibit its activity, they are weaker inhibitors than aspirin.

# ADRS.....

- ▶ Aspirin-induced gastric bleeding sometimes is painless and, if unrecognized, may lead to iron-deficiency anemia.
- ▶ The daily ingestion of anti-inflammatory doses of aspirin (3-4 g) results in an average fecal blood loss of between 3 and 8 mL/day, as compared with ~0.6 mL/day in untreated subjects.
- ▶ Salicylates can cause hepatic injury, usually in patients treated with high doses of salicylates that result in plasma concentrations of >150 µg/mL.

# ADRS.....

## ▶ **Metabolic Effects:**

- ▶ Large doses of salicylates may cause hyperglycemia and glycosuria and deplete liver and muscle glycogen; these effects are partly explained by the release of epinephrine.
- ▶ Such doses also reduce aerobic metabolism of glucose, increase glucose-6-phosphatase activity, and promote the secretion of glucocorticoids.
- ▶ Salicylates reduce lipogenesis by partially blocking incorporation of acetate into fatty acids.

# ADRS.....

## ▶ **Uricosuric Effects:**

- ▶ The effects of salicylates on uric acid excretion are markedly dependent on dose.
- ▶ Low doses (1 or 2 g/day) may decrease urate excretion and elevate plasma urate concentrations; intermediate doses (2 or 3 g/day) usually do not alter urate excretion.
- ▶ Large doses (>5 g/day) induce uricosuria and lower plasma urate levels; however, such large doses are tolerated poorly. Even small doses of salicylate can block the effects of probenecid and other uricosuric agents that decrease tubular reabsorption of uric acid.

# ADRS.....

## ▶ **Effects on the Blood:**

- ▶ Patients with severe hepatic damage, hypoprothrombinemia, vitamin K deficiency, or hemophilia should avoid aspirin because the inhibition of platelet hemostasis can result in hemorrhage.
- ▶ Salicylates ordinarily do not alter the leukocyte or platelet count, the hematocrit, or the hemoglobin content. However, doses of 3-4 g/day markedly decrease plasma iron concentration and shorten erythrocyte survival time.
- ▶ Aspirin can cause a mild degree of hemolysis in individuals with a deficiency of glucose-6-phosphate dehydrogenase.

# ADRS.....

- ▶ **Endocrine Effects:**
- ▶ Long-term administration of salicylates decreases thyroidal uptake and clearance of iodine, but increases O<sub>2</sub> consumption and the rate of disappearance of thyroxine and triiodothyronine from the circulation. These effects probably are caused by the competitive displacement by salicylate of thyroxine and triiodothyronine from transthyretin and the thyroxine-binding globulin in plasma.
- ▶ **Ototoxic Effects.** Hearing impairment, alterations of perceived sounds, and tinnitus commonly occur during high-dose salicylate therapy.

# ADRS.....

- ▶ **Salicylates and Pregnancy:**
- ▶ Infants born to women who ingest salicylates for long periods may have significantly reduced birth weights. When administered during the third trimester, there is also an increase in perinatal mortality, anemia, antepartum and postpartum hemorrhage, prolonged gestation, and complicated deliveries; thus, its use during this period should be avoided.
- ▶ Administration of NSAIDs during the third trimester of pregnancy also can cause premature closure of the ductus arteriosus.



# Drug-drug interaction

## ▶ **Drug Interactions:**

- ▶ The plasma concentration of salicylates generally little affected by other drugs, but concurrent administration of aspirin lowers the concentrations of indomethacin, naproxen, ketoprofen, and fenoprofen, by displacement from plasma proteins.
- ▶ Aspirin with warfarin prolong bleeding time.
- ▶ Aspirin antagonises spironolactone-induced natriuresis.



# Drug-drug interaction.....

- ▶ Blockade of the active transport of penicillin from CSF to blood.
- ▶ Magnesium-aluminum hydroxide antacids can alkalize the urine enough to increase salicylic acid clearance significantly and reduce steady-state concentrations.
- ▶ Aspirin also may antagonize the effects of sulphonylureas.

# Management of Salicylate Overdose

- ▶ Salicylate poisoning represents an acute medical emergency.
- ▶ Monitoring of salicylate levels is a useful guide to therapy but must be used in conjunction with an assessment of the patient's overall clinical condition, acid–base balance, formulation of salicylate ingested, timing, and dose.
- ▶ Poisoning occur with aspirin when level exceeds 150-175mg/kg.
- ▶ There is no specific antidote for salicylate poisoning.
- ▶ Management begins with a rapid assessment followed by the ABCD, gastric lavage and administration of sodium bicarbonate solution.

# Propionic acid derivatives

## ▶ **Ibuprofen**

- ▶ First member of propionic acid derivatives Introduced in 1969, over the counter drug
- ▶ Non-selective reversible inhibitors of COX enzymes.
- ▶ It is well absorbed orally; peak serum concentrations are attained in 1 to 2 hours after oral administration.
- ▶ It is rapidly bio-transformed with a serum half life of 1.8 to 2 hours.
- ▶ The drug is completely eliminated in 24 hours after the last dose and eliminated through metabolism.

# Ibuprofen.....

- ▶ The drug is more than 99% protein bound, extensively metabolized in the liver and little is excreted unchanged.
- ▶ Undergo entero-hepatic circulation.
- ▶ Plasma concentration may decrease with milk or food.
- ▶ More than 90% of an ingested dose is excreted in the urine as metabolites or their conjugates, the major metabolites are hydroxylated and carboxylated compounds.
- ▶ Has more potent anti-inflammatory effect than aspirin.
- ▶ Ibuprofen(2400mg daily dose=4g of aspirin).
- ▶ Effective in closing patent ductus arteriosus in preterm infants with equal efficacy to indomethacin and with less ADRS.

# Ibuprofen.....

- ▶ Effective in post dental surgical pain
- ▶ Cause less fluid retention than indomethacin
- ▶ Dose: in children 100-200mg 3 to 4 times a day
- ▶       in adults 300-400mg 3-4 times a day
- ▶ Recemic ibuprofen and S(+) enantiomer are mainly used in the treatment of mild to moderate pain related to dysmenorrhea, headache, migraine, postoperative dental pain, management of spondylitis, osteoarthritis, rheumatoid arthritis and soft tissue disorder.
- ▶ *Cystic fibrosis (CF)*: High dose ibuprofen therapy has also been shown to be effective in decreasing inflammation, probably by decreasing polymorphonuclear cell influx into the lungs.

# Ibuprofen.....

- ▶ Ibuprofen was significantly more effective than paracetamol in lowering temperatures throughout the first 4-5 hrs after dosing and thus should be considered as an antipyretic agent in the management of uncomplicated falciparum infections.
- ▶ *Prophylaxis of Alzheimers disease*: The administration of NSAIDs, particularly ibuprofen markedly reduced neurodegeneration
- ▶ Ibuprofen antagonizes /block the irreversible platelet inhibition by aspirin

# Ibuprofen.....

- ▶ Contraindicated in nasal polyps, angioedema, bronchospastic reactivity to aspirin
- ▶ Although highly bound to plasma proteins (90-99%), displacement interactions are not clinically significant, hence the dose of oral anti-coagulants and oral hypoglycemic needs not be altered
- ▶ The major adverse reactions include the affects on the gastrointestinal tract (GIT), the kidney and the coagulation system.
- ▶ Other effects include thrombocytopenia, rashes, headache, dizziness, blurred vision