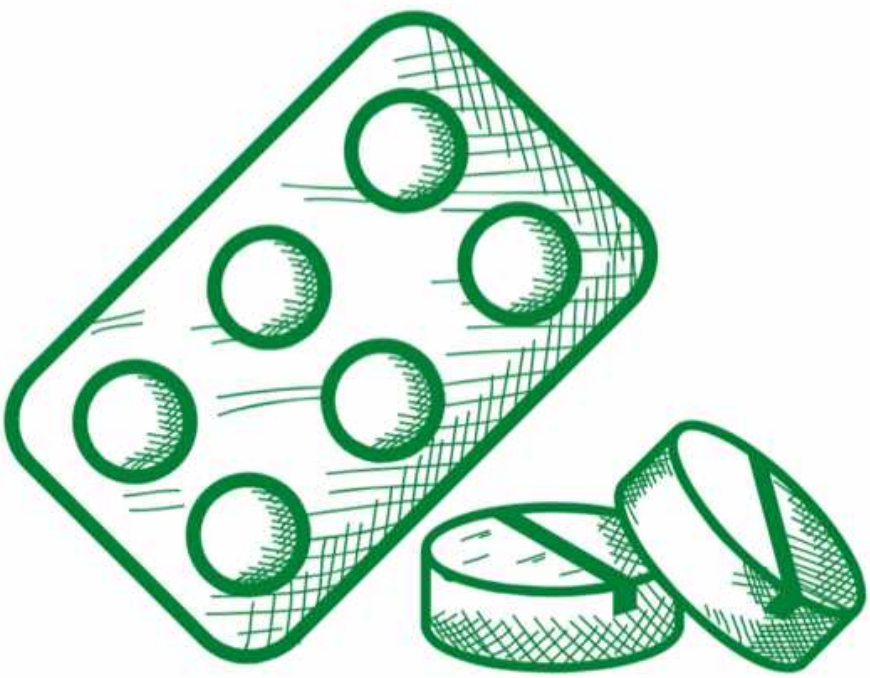
MSS

Sheet no.

Pharmacology



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Doctor:

Aspirin

What makes aspirin a special drug!

- It's the only one that has an anti platelet effect with regard to these drugs
- It's slightly selective to cox1
- It's the prototype of traditional NSAIDs
- Most common used any new drug is mostly compared to it

At first they thought that NSAIDs are non selective but with some SE they noticed some kinda selectivity for receptors

MOA

(Considered weak organic acid) an irreversible inhibitor for(cox1&cox2 while all other NSAIDs are reversible

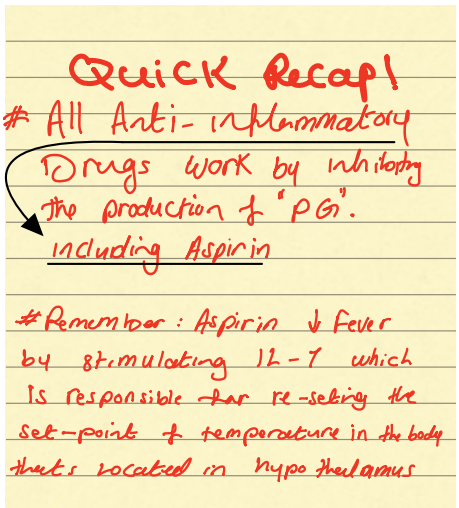
It's rapidly deacetylated by esterase in the body producing **salicylate** which has

1. Anti inflammatory
2. Antipyretic

these 2 effects are due to the **blockade of PG synthesis** at the thermoregulatory centers in the hypothalamus & peripheral target sites

Antipyretic mainly by

- **re-setting the set point of temperature**
- higher doses lowers the temperature of febrile patients by ⬆️ heat dissipation as a result of **peripheral vasodilation** and sweating (VSMC)—it relaxes vascular smooth muscle cells leading to vasodilation thus decreasing the temperature



Note:resetting the set point of temperature doesn't change the normal body temperature

Note: Elevating the set point—means Fever

3. Analgesic effect

Beside decreasing PG synthesis ,salicylate also prevents the sensitization of pain receptors to both(chemical and mechanical effect)

In addition to that aspirin has shown an effect on depressing pain stimuli at **subcortical** sites

Respiratory action:

- **At therapeutic doses,** aspirin increases alveolar ventilation. uncouple oxidative phosphorylation, which leads to elevated CO2 and increased respiration.
- **Higher doses** work directly on the respiratory center in the medulla, resulting in hyperventilation and respiratory alkalosis
- **At toxic levels**, central respiratory paralysis >> acidosis

Toxicity of salicylates

(1) stimulation of the respiratory center of the brain, leading to hyperpnea and respiratory alkalosis
(2) uncoupling of oxidative phosphorylation, leading to increased oxygen utilization and glucose demand, increased oxygen utilization and glucose demand, increased glyconeogenesis, and increased heat production
(3) inhibition of Krebs cycle enzymes, leading to decreased glucose availability and increased organic acids
(4) alterations in lipid metabolism and amino acid metabolism, enhancing metabolic acidosis
(5) increased fluid and electrolyte losses, leading to dehydration, sodium depletion, potassium depletion, and loss of buffer capacity.

Solutions

- To correct the acidosis—(Alkalization for urine)we've talked about it in general pharma
- Fix the electrolytes and fluids
- Need to be careful regarding patients who have sensitivity for salicylate (salcylism)

#U see nowadays most ppl take baby aspirin(low dose) for history in having thrombosis & to avoid having MI or stroke in the near future.
#Aspirin toxicity effect(liver &CNS)on children is called **Reye's syndrome**
#In Viral infections aspirin is contraindicated for children

Gastrointestinal effects:

- PGE2 stimulate synthesis of protective mucus in both the stomach and small intestine.
- In the presence of aspirin, these prostanoids are not formed, resulting in **increased gastric acid** secretion and **diminished mucus protection.**
- In long term prescription of it,it will result in **gastric ulcers** so —Agents used for the prevention of gastric and/or duodenal ulcers include proton-pump inhibitors (PPIs) preferred ones; esomeprazole, lansoprazole, omeprazol , antihistamine (H2),Misoprostol is a (analog prostaglandin but it's not preferred for having many SE)
- At stomach pH, aspirin is uncharged; consequently, it readily **crosses into mucosal cells, where it ionizes (becomes negatively charged) and becomes trapped**, thus potentially causing direct damage to the cells

Note:changing the route of administration doesn't lower the degree of the SE but taking the drug on full stomach is much safer for protecting ur gastric cells from damage

Effect on platelets:

- TXA2(produced by COX1 that's why it's more selective for it) enhances platelet aggregation >> Low doses 81 mg daily of aspirin can **irreversibly inhibit** thromboxane production in platelets via acetylation of cyclooxygenase.
- Because platelets lack nuclei, they cannot synthesize new enzyme, and the lack of thromboxane persists for the lifetime of the platelet (7 days)(because platelets lack nucleithey cannot synthesis a new enzymes it means u gotta wait ur body to make a new cells) >> As a result prolonged bleeding time.

Actions on the kidney:

- Cyclooxygenase inhibitors prevent the synthesis of PGE2 and PGI2 that are responsible for maintaining **renal blood flow.**
- Decreased synthesis of prostaglandins can result in **retention of sodium and water and** may cause edema and hyperkalemia in some patients.
- **Interstitial nephritis** can also occur with all NSAIDs but less with aspirin (specially at low dose)

Note:most of NSAIDs play with renin-angiotensin effect leading to hypertension,while aspirin has the least effect even at low doses moreover most of NSAIDs cause nephrotoxicity while it's least expected in aspirin

Note:don't forget that we also use aspirin for prophylactic effect at 81-100mg up to 300mg is still selective for cox1 but the general rule in pharmacodynamic says ~if u increase the dose ur gonna loose the selectivity which means anti platelets effect needs higher dose than that in the prophylactic effect

Therapeutic uses

- The salicylic acid derivatives are used in the treatment of **inflammatory conditions** (gout, rheumatic fever, osteoarthritis, and RA)
- Commonly treated conditions requiring **analgesia** include headache, arthralgia, and myalgia.

External applications:

- Salicylic acid is used **topically to treat corns and warts.**

Cardiovascular applications:

- Aspirin is used to inhibit platelet aggregation. Low doses are used prophylactically to
- reduce the risk of recurring transient ischemic attacks (TIAs) and stroke or death
- Studies have shown a reduced risk of death in those having an acute myocardial infarction or angina attack (it's caused by vasospasm of BV (bronchospasm) or atherosclerosis which is (lipid deposition in BV)

PHARMACOKINETICS

Administration and distribution:

- After oral administration,the un-ionized salicylatesare

passively absorbed from the stomach and the small intestine

- Rectal absorption of the salicylates is slow and unreliable ,but

it is a useful route for administration to vomiting children.

- Salicylates must be avoided in children and teenagers (<15 years old) with varicella (chickenpox) or influenza to prevent Reye's syndrome.
- Salicylates are highly protein bound mainly (albumin) this indicate a risk for drug-drug interaction so be carful about another protein bound drug combination

Ex;prescription of Phenytoin(anti-epilepsy) with aspirin there's gonna be a competition on albumin so phenytoin will be displaced in the blood causing nephrotoxicity ,and this is applied on any other protein bound drug

Dosage:
The salicylates exhibit analgesic activity at low doses; only at higher doses do these drugs show anti-inflammatory activity .

- For example, two 325-mg aspirin tablets administered four times daily produce analgesia, whereas 12 to 20 tablets per day produce both analgesic and anti-inflammatory activity we need higher dose but we still worry about it resulting in GI
- Forlong-termmyocardialinfarctionprophylaxis,thedoseis 81 to 162 mg/day
- for those with RA or osteoarthritis,the initial dose is3 grams/day
- for stroke prophylaxis, the dose is 50 to 325 mg/day

Metabolism and excretion

- At dosages of 650 mg/day, aspirin is hydrolyzed to salicylate and acetic acid by esterases in tissues and blood .
- Salicylate is converted by the liver to water-soluble conjugates that are rapidly cleared by the kidney
- Both hepatic and renal function should be monitored periodically in those receiving long-term, high-dose aspirin therapy.
- aspirin should be avoided in patients with a creatinine clearance of less than 10 mL/min.

Other side effects

Hypersensitivity: Approximately 15 percent of patients taking aspirin experience hypersensitivity reactions.

- Symptoms of true allergy include urticaria, bronchoconstriction, or angioedema. Fatal anaphylactic shock is rare & once reaches the CNS it causes sonitus and imbalance

Reye's syndrome:

- Aspirin and other salicylates given during viral infections has been associated with an increased incidence of Reye's syndrome, which is an often fatal, fulminating hepatitis with cerebral edema.
- This is especially encountered in children, who therefore should be given acetaminophen instead of aspirin

It can cause hepatitis ,cerebral edema and encephalopathy so the recommended drug for fever in children is acetaminophen

Drug interactions:

- Salicylate is 90 to 95 percent protein bound and can be displaced from its protein-binding sites, resulting in increased concentration of free salicylate
- alternatively, aspirin could displace other highly protein-bound drugs, such as warfarin(anticoagulant), phenytoin(anti epilepsy), or valproic acid(anti epilepsy), resulting in higher **free** (active drug that's giving the effect)concentrations of the other agent .
- Concomitant use of ketorolac and aspirin is contraindicated because of increased risk of GI bleeding and platelet aggregation inhibition.

Note; additive effect on the therapeutic effect is not used it makes it worse

Aspirin and pregnancy

- In pregnancy: Aspirin is classified as FDA pregnancy category C risk during Trimesters 1 and 2
- category D during Trimester 3 (7,8,9)

ductus arteriosus;it's like a shunt during the fetus life for not using the lungs so taking aspirin is gonna decrease PG & this can increase the chance of its closure but after birth it has to be closed otherwise(still open) it's called patent ductus arteriosus we can use NSAIDs(ibuprofen or Indomethacin but not aspirin) to maintain the closure if that didn't work, the baby needs a surgery

- Because salicylatesare excreted in breast milk, aspirin should be avoided during pregnancy and while breast- feeding.

#Pregnancy categories:

According to researcher explanation

A; safest like paracetamol

B:studied on animals &didn't show a lot of SE

C; studied on animals but shows SE on fetus

D; studied in unmans and we're sure that this drug has some SE but not contraindicated, we assist the benefit ratio from it

contraindicated

X: like isotretinoin & thalidomide

Note; Aspirin increase the vascularization thus increase the fertility &decrease the chance of implantation

Reye's syndrome

• Reye's syndrome is a potentially fatal disease that has numerous detrimental effects to many organs, especially the brain and liver, as well as causing a lower than usual level of blood sugar (hypoglycemia) The classic features are a rash, vomiting, and liver damage. The exact cause is unknown and, while it has been associated with aspirin consumption by children with viral illness, it also occurs in the absence of aspirin use.

Me waiting to reach the "thank u "slide:

Propionic acid derivatives

- Ibuprofen , naproxen, fenoprofe, ketoprofen , flurbiprofen All these drugs possess anti-inflammatory, analgesic, and antipyretic activity
- their GI effects are generally less intense than those of aspirin. Thesedrugsarereversibleinhibitorsofthecyclooxygenases
- All are well absorbed on oral administration and are almost totally bound to serum albumin.
- They undergo hepatic metabolism and are excreted by the kidney.
- The most common adverse effects are GI, ranging from dyspepsia(increase the ulcer secretion) to bleeding.
- Side effects involving the central nervous system (CNS), such as headache, tinnitus, and dizziness, have also been reported

- The use of sulindac has also been linked to cases of acute pancreatitis.The use of dimethylsulfoxide (DMSO) topically in combination with sulindac has been reported to induce severe neuropathy

Naproxen and Ibuprofen

- Pregnancy : category C, category D from
- Increase the risk of cardiovascular thrombotic event, MI and

stroke. Except for aspirin

- Increase risk of GI bleeding.
- Ibuprofen not exceed 3200mg/day., and take with food or with water to avoid GI effect.
- Asthmatic patient.

Acetic acid derivatives

Indomethacin , sulindac , Etodolac

- All have anti-inflammatory, analgesic, and antipyretic activity. They act by reversibly inhibiting cyclooxygenase.
- Despite its potency as an anti-inflammatory agent, the toxicity of indomethacin limits its use to the treatment of acute gouty arthritis, ankylosing spondylitis .
- The adverse reactions caused by sulindac are similar to, but less severe than, those of the other NSAIDs, including indomethacin.
- Etodolac has effects similar to those of the other NSAIDs

Note ;chemical groups are not required

لو دخلت صيدله شو
كان حيصير!

Indomethecin

- acute and chronic rheumatoid arthritis and osteoarthritis.
- Also useful in ankylosing spondylitis, acute gouty arthritis, bursitis, and tendinitis.

Side effects:

1. It produces more CNS side effects than most of the other NSAIDs. Severe headache occurs in 25 to 50% of patients; vertigo, confusion, and psychological disturbances
2. GI symptoms also are more frequent.
3. Hematopoietic side effects (e.g., leukopenia, hemolytic anemia, aplastic anemia, purpura, thrombocytopenia, and agranulocytosis
4. Ocular effects (blurred vision, corneal deposits) Hepatitis, jaundice, pancreatitis, and hypersensitivity reactions but these are less rare

Note:Phenylbutazone is also a NSAIDs but it's rarely used due to causing agranulocytosis SE

Oxicam derivatives

Piroxicam and meloxicam

- are used to treat RA, ankylosing spondylitis, and osteoarthritis.
- They have **long half-lives**, which permit once-daily administration, and the parent drug as well as its metabolites are renally excreted in the urine.
- **Meloxicam** inhibits both COX-1 and COX-2, with preferential binding for COX-2, and at low to moderate doses shows less GI irritation than piroxicam.

Fenamates

Mefenamic

- have no advantages over other NSAIDs as anti-inflammatory agents.
- Their side effects, such as diarrhea, can be severe, and they are associated with inflammation of the bowel.
- Cases of hemolytic anemia have been reported

Heteroaryl acetic acids

- **Diclofenac** and **tolmetin** , **ketorlac**
- are approved for long-term use in the treatment of RA, osteoarthritis.
- Diclofenac is more potent than indomethacin or naproxen.
- An ophthalmic preparation is also available.
- Diclofenac accumulates in synovial fluid, and the primary route of excretion for the drug and its metabolites is the kidney.

Diclofenac sodium

- Used PO 50mg after food, I.M. inj 75mg
- Diclofenac potassium is prompt release and has quicker onset where as the Diclofenac sodium is delayed release.
- Pregnancy: category C

Diclofenac sodium

- C/I
- Hypersensitivity.
- Asthmatic patient.
- Patient with history of peptic ulcer.
- Metabolism: liver.
- Excretion: urine.

The doc skipped like 5 slides ,I put them here but I have no idea If she's gonna talk about them later or not, so thank u for ur hard working,and studying all these drugs, and to remind u "u have to do ur best" so ppl can trust u❤️

Wish me luck