NSAIDS (1)

Lecture
Inflammation is triggered by the release of chemical mediators from injured tissues and migrating cells. The specific mediators vary with the type of inflammation. They include:

1. Amines (Histamine, 5HT)
2. Lipids (PGs)
3. Small peptides (bradykinin).
4. Large peptides (IL-1)

- Drags that act on certain mediators will not affect the inflammation process involving other mediators.

- **Many NSAIDs act by inhibiting the synthesis of PGs.** PGs and related eicosanoids are released in minute amounts by all tissues except RBCs, they are synthesized and inactivated in and same place so the circulating level is very small (i.e. PGs don't circulate in blood in significant level).

- NSAIDs are group of dissimilar agents, they differ in the following activities:
  1. Antipyretic effect.
  2. Analgesic effect.
  3. Anti-inflammatory effect.

- **NSAIDs act by inhibiting the enzyme cyclo-oxygenase (COX), the prototype of this group is Aspirin,** the most commonly used and the drug to which all other anti-inflammatory agents are compared. 15% of patients show intolerance to aspirin, they may benefit from other NSAIDs. Some of the newer NSAIDs are better than Aspirin in certain patients either because of less gastric irritation of standard anti-inflammatory action or can be taken less frequently, **but** they are still more expensive than Aspirin and some are more toxic.

Aspirin and Salicylates
Aspirin is a weak organic acid irreversibly acetylate (inactivate) Cox , mainly COX-1, while other NSAIDs, including salicylates are reversible inhibitors for COX enzyme.

Aspirin is rapidly deacetylated by Esterase to produce salicylates with are still active (have anti-inflammatory, Antipyretic and Analgesic effects).

**Kinetics:**

- Salicylates are rapidly absorbed from the stomach and upper part of the small intestine yielding a peak plasma conc. within 1-2 hrs.
- *The acidic medium in the stomach (PH= 1.5)* keeps large fraction of salicylates in non-ionized from (lipid soluble) so it diffuses easily and absorption is promoted.
- when high conc. of salicylates enter the mucosal cells, the drug may damage the mucosal barrier and result in gastric ulcer. If gastric PH is raised by suitable buffer to 3.5 or higher gastric irritation will be minimized (less absorption → less irritation).
- After absorption of aspirin it is hydrolyzed into acetic acid and salicylates, salicylate binds to albumin but as serum conc. of salicylates increases, a greater fraction remain unbound and available to tissue.
- Ingested salicylates and that generated by hydrolysis of aspirin may excreted unchanged, but most is converted to water soluble conjugates that are rapidly cleared by the kidney. When this pathway becomes saturated, a small increase in aspirin dose result in large increase in plasma level.*
- Urine alkalinization will prevent reabsorption of salicylates.
- When aspirin is used in low doses (less than 600 mg) then it will follow the 1st order kinetics (t\(_{1/2}\) 3-5 hrs), while at higher doses it will follow zero order kinetics (t\(_{1/2}\)= 15 hrs).
- The t\(_{1/2}\) also depends on the status of the kidney and liver. The ↑ in t\(_{1/2}\) (at high aspirin doses) → occurs about after week (till the saturation of the hepatic enzymes) that will lead to the formation of
calicyluric conversion compounds salicyl phenylglucuronide and salicyluric acid.

* see the diagram in the next page.

Metabolism of Aspirin:

Dynamics "Action of Aspirin & salicylates"

1) Anti-inflammatory effect:
The effectiveness of Aspirin is largely due to its capacity to inhibit PGs synthesis. It irreversibly blocks enzyme COX which catalyze the reaction of AA to cyclic endoperoxide compounds.

- In high doses, Aspirin ↓ the formation of PGs and TXs (TXA₂).
- It also interferes with chemical mediators of Kallikrein synthesis.
- It inhibits granulocytes adherence to damaged vasculature and stabilizes lysosomes and inhibits migration of polymorphonentrophils (PMN) WBCs & macrophages to site of inflammation.
2) **Analgesic effect:**

- Aspirin is the most effective in reducing pain of mild to moderate intensity *(not severe pain)*.
  - It alleviates pain of varying causes: muscular, dental post parum, arthritis and bursitis. **But it is not useful for visceral pain.**
  - Aspirin acts *peripherally* through its effect on inflammation but probably also *depresses* pain stimulation at a subcortical level site.
  - By ↓ *PGE$_2$ synthesis*, Aspirin and other NSAIDs depress sensation of pain.
  - NSAIDs are superior to opioids is the management of pain due to inflammation. *(have max. efficacy more than that of opioids).*
  - NSAIDs are combined with opioids in treating pain in malignancy.

3) **Anti-pyretic effect:**

- Aspirin decreases (↓) elevated temperature *in case of fever* whereas normal body temperature is only slightly affected.
- The fall in temperature is related to increased dissipation of heat caused by vasodilation of the superficial blood vessels. Anti-pyresis may be combined sweating.
  The fever associated with infection is through to result from 2 action:

a) from production of PG in the CNS in response to bacterial pyogens.

b) through the effect of IL-1 on hypothalamus (IL-1 is produced during inflammation by macrophages to activate lymphocytes but ↑ temp).
  - Aspirin blocks the CNS response to IL-1, so it may reset the temp. control
  - in hypothalamus thereby facilitating heat dissipation by vasodilation.
4) **Anti-platelet effect:**

- Aspirin affects hemostasis, single dose aspirin produces a slightly prolonged bleeding time which doubles if administration is continued for a week.
- *This change is explained by inhibition of platelets aggregation, secondarily to inhibition of TXA\textsubscript{2} synthesis* (*TXA\textsubscript{2} accelerates platelet aggregation*).  
- Aspirin inhibits platelet aggregation up to 8 days till the formation of new platelet.*  
- Aspirin has long duration of action when compared with other agents used to inhibit platelet aggregation such as: clofibrate, phenylbutazone, dipyridamole.

* platelet life span 8 days, thus continuous anti-platelet effect is readily achieved with low doses.

5) **Respiratory Effect:**

*Therapeutic does* ↑ alveolar ventilation, *higher does* acts directly on respiratory centre (in medulla) causing hyperventilation and respiratory alkalosis, *toxic dose* cause central respiratory paralysis and metabolic acidosis, due to continuous CO2 production.

6) **GIT effects:**

*PGI\textsubscript{2}* inhibits gastric secretion, *PGE\textsubscript{2}* stimulates synthesis of protective mucosa in the stomach and intestine.

- **In presence of Aspirin,** both *PGI\textsubscript{2} and PGE\textsubscript{2*} are not formed and this will lead to ↑ gastric acid secretion and ↓ mucous production → so this may cause: *epigastric distress, ulceration and hemorrhage.*  
- With ordinary doses of Aspirin, **3-8 ml of blood** may be lost with feces every
day.
- Buffered and Enteric coated Aspirin preparations, that delay absorption of aspirin to the upper small intestine, are only partially helpful and more expensive.
- Misoprostol (PGE derivative) is used for treatment of gastric damage induced by NSAIDs.

7) Action on kidney:
Inhibition of COX prevents the synthesis of PGI₂ and PGE₂ which are responsible for maintaining normal renal blood flow (especially in the presence of vasoconstrictors)
Diminished synthesis of above PGs can result in Na⁺ and water retention causing edema and hypokalemia in some patients.

Clinical uses of Aspirin:

1. Analgesic and anti inflammatory:
   I. Analgesic effect:
   - Aspirin most frequently is used to reduce mild to moderate pain.
   - Aspirin may be combined with other analgesics (as opioids) and called as OTC drugs (out of the counter drugs that are solid with prescriptions).
   - These combination are not more effective or less toxic than aspirin but they are only more expensive. The disadvantage of these
combinations is that poisoning with them is difficult to treat because we don't know exactly what member is the true cause of poisoning.

- Aspirin is not effective in the treatment of visceral pain such as (acute abdomen, MI, or renal colic).

II. *anti-inflammatory action* of salicylates in *high dose* are responsible for their recommendations as initial major therapy in *rheumatoid arthritis, acute rheumatic fever* and other inflammatory conditions.

2. *Other indication:*

   a) *Antipyretic:* aspirin is the best available drug for ↓ fever.

   b) *Inhibition of platelet aggregation:* aspirin used in ¹) *transient ischemic attacks* (TIAs) and ²) *unstable angina*.

   c) *External application:* salicylic acid is used topically for treatment of corns and calluses epidermititis.

   - Methyl salicylic acid (oil of wintergreen) is used externally as counter irritant in ointments.