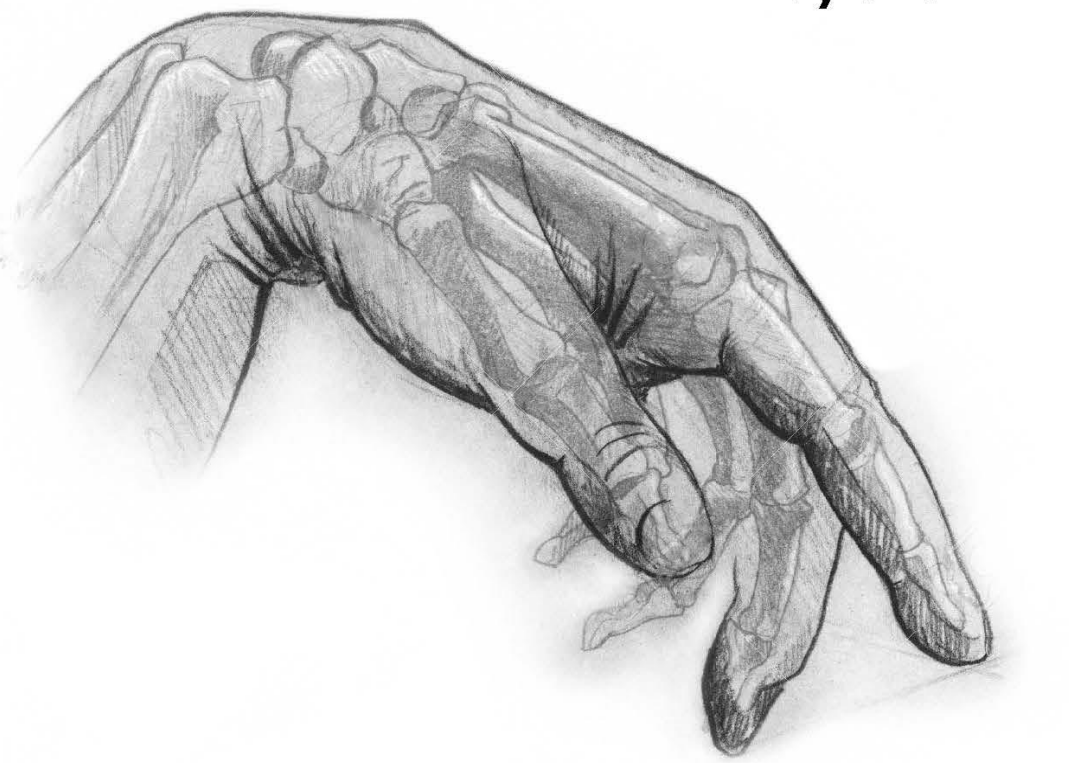
The

Musculoskeletal

System



Pharmacology

☑ Sheet ☐ Slide ☐ Handout

Number:	2
Subject:	NSAIDs and aspirin
Done By:	Rafa'a Alma'ani
Corrected By:	Anas Mourad
Doctor:	Dr.alia shatnawi

Date: 0/00/0000

Price: .....

Quick review,

An Inflammation is a protective response to a tissue injury; Caused by physical trauma, chemicals, or microbiological agents.

It's also the body's response to get rid of that agent and set the stage for tissue repair.

When there are acute or chronic conditions where pain and inflammation are present…we use non-steroidal anti-inflammatory drugs (NSAID).

The doctor also mentioned that: Some of them have probability to increase the uric acid excretion.

They act primarily by inhibiting the cyclooxygenase enzymes "with its two isoforms" and this will lead to a decrease in the production of prostaglandins, with both beneficial and unwanted effects.

Differences in safety and efficacy of these drugs are related to their selectivity for inhibiting COX-1 or COX-2.

NSAID have three major therapeutic effects, they **reduce:**

- Inflammation (anti-inflammatory).
- Pain (analgesic effect).
- Fever (anti-pyretic effect).

review is end

Remember…prostaglandins are unsaturated fatty acid derivatives, containing 20 carbons with a cyclic ring structure.

They are synthesized from their primary precursor; (arachidonic acid) by action of cyclooxygenase enzymes.

We said that certain prostaglandins can:

1) **Cause vasoconstriction (PRO.E):**
   So, if we oppose vasoconstriction in the blood vessels "asthma" we will end with vasodilation which produces edema. So, when we inhibit prostaglandins that cause edema we will have less edema and less of the inflammatory consequences of edema or swelling.

2) **Cause vasodilation:**

When we have headache, we have vasodilation of the blood vessels "cerebral arteries" and this can be caused by prostacyclin (PRO.I). So, when we inhibit the prostaglandin we inhibit the vasodilation of these arteries in the brain decreasing the pain "The Headache".

3) **Stimulate the production of many cytokines:**

Cytokines activate certain adhesion molecules in the cells leading to an inflammatory reaction. So, by inhibiting prostaglandins we can prevent the formation of adhesion molecules thus inhibiting the recruitment of more leukocytes and inhibiting the perpetuation of the

(Remember pathology in the last semester "for the inflammatory process to happen, we have the leukocytes in our blood stream and when we have certain stimuli at a certain cite so we recruit them to the inflammatory site which in turn produces adhesion molecules for the leukocytes to get stick to them so they bind these adhesion molecules and then they get internalize "producing the stimuli")

inflammatory process.

The three major therapeutic effects of NSAID:

1) **How do they reduce pain?**

Prostaglandins are thought to sensitize nerve endings toward the action of (bradykinin, histamine and other mediators), which are released by inflammation.

So, when we reduce the synthesis of prostaglandins by NSAID, sensation to pain will be decreased as well "because of less sensitivity to nerve endings toward nociception of pain".

We don't decrease these receptors centrally "that give us the signal of pain" but we work on the peripheral nerve ending and we decrease threshold of pain.

Pain is number ONE why people take medications; NSAIDs are used mainly for the management of mild to moderate pain.

Remember: the headache relief mechanism mentioned above.

2) How do they reduce fever? "The anti-pyretic effect"

Prostaglandins don't reduce the fever in normal individual so for example if we give the patient an Ibuprofen it'll not decrease his temperature on the other hands it works on elevating temperature.

The thermal regularity control centers in our bodies are found in the hypothalamus so certain mediators (don't affect prostaglandins directly) "Interleukin-1" is secreted from certain leukocytes can affect these centers and increase the temperature set point "Increases the body temperature".

TO sum up:

- Fever occurs when the set-point in hypothalamic thermoregulatory center is elevated. And that can be caused by action of prostaglandins (stimulated by agents released from WBC's).

- The NSAIDs "for example ***Aspirin***" prevents the temperature rising effect of (**IL-1**) by the impeding of prostaglandin synthesis.

- *You can see here that we have different effects that are produced by the inhibition by cyclooxygenase*

Remember NSAIDs have NO effect on normal body temperature.

Adverse effects of NSAIDs:

- The most common adverse effect of NSAIDs is gastrointestinal related. BUT how?? Prostaglandins normally stimulate the synthesis of protective mucus in both stomach and small intestines. Group of drugs that inhibit **cox-1** pathway will reduce the beneficial levels of these PGs. So that will result in:

1- Increased gastric acid secretion.
2- Diminished mucus production.

Increased risk for GI damage “bleeding and ulceration”.

Note:

a) Drugs with higher selectivity for COX-1 may have higher risk for GI events mentioned above.
b) The table in slide 20 is not for memorization just focus on the drugs that we are going to discuss them later in details
   1- Nonselective COX inhibitors:
   (Diclofenac, Indomethacin, Piroxicam, Naproxen, Ibuprofen, Aspirin).
   2- Selective COX-2 inhibitors:
   (Celecoxib, Rofecoxib).

- Other side effect caused by NSAIDs which **is increased risk of bleeding**

NSAIDs inhibit production of thromboxane“COX-1-derived” TXA2, and because of that decrease in TXA2 production, platelet aggregation is reduced and we will end by producing an anti-platelet effect with prolonged bleeding time.

- Aspirin “An anti-platelet drug” irreversibly inhibits COX1 enzyme, and for that reason the lack of thromboxane will persist for the lifetime of the platelet (8-11) days. And that’s why aspirin is often held or not given at least one week prior to surgery.

- Agents such as Aspirin have shown a cardiovascular protective effect due to the reduction in TXA2 synthesis “And that’s why we use it prophylactically with patients having certain cardiovascular problems”. However, other drugs with selectivity toward COX2 associated with increased risk of cardiovascular events like stroke, ischemic heart attacks and MI (myocardial infarction).

Aspirin ..

Aspirin is a prototype for all NSAIDS ..

Pharmacodynamics:

Remember that aspirin binds COX1 irreversibly and acts as a non-competitive inhibitor.(until the cell dies off)

All other NSAIDA bind reversibly.

Meaning once Salicylate is bound to the platelet it inhibit its Function permanently.
The difference between a platelet and a normal cell is the nucleus, If platelets have nucleus they would regenerate COX enzyme and the binding won't be irreversible.

1-Effects on cardiovascular system

-Prostaglandins, generally, antagonize the effect of epinephrine and angiotensin.
Epinephrine and angiotensin tend to elevate BP. Prostacyclin causes vasodilation , opposing the effect of epinephrine and angiotensin , reducing BP.
Aspirin will inhibit prostacyclin, this may **elevate the blood pressure in some patients**.

Note: Angiotensin2 is a peptide produced by the body and causes vasoconstriction, while epinephrine “Adrenalin” and nor-epinephrine are produced in the adrenal medulla and also they are produced centrally in the brain they cause activation of the sympathetic nervous system in which it raises the blood pressure through stimulating the vascular smooth muscles.

- in relation to atherosclerosis ، Aspirin may cause a rupture of these plaques, this may lead to **embolism** , meaning that this clot can move through blood vessels and if it reached a small artery it can occlude it. (If it goes to the heart it can cause myocardial infarction and if it goes to the to the brain it can cause stroma.)

Remember that NSAIDs can also inhibit the activity of TXA2 , so :

- Aspirin is used mainly as prophylactic drug.

- reduces risk of ischemic heart injury or stroke.

-reduces risk of death in patients with myocardial infarction or angina.

2-effects on renal system

Aspirin is safe to use in almost all patients but there are exceptions like in patients who have renal problems. But WHY?

-Usually prostaglandins increase glomerular filtration rate in kidneys. So when we use these drugs we put the patients at risk of elevating their blood pressure (filtration of ions is decreased).

3-Effect on GI system:

Again, prostaglandins inhibit acid secretions and stimulate mucus secretion so they play a protective role in stomach. if we inhibited prostaglandins, everything will be reversed. Meaning we will have more acid secretion and less protection by mucus. Ending with **gastritis** or **gastric bleeding** if ulcer happens.

One of the solutions for this problem is using **misoprostol**. Misoprostol is a prostaglandin analog so that it mimics the effect of prostaglandin. So it can protect our stomach cells.

However, this drug is contraindicated in pregnant women. Because it will cause premature contractions in the uterus leading to abortion.

4-Effect on uterus:

prostaglandins cause contractions of uterine muscles so they can be used to induce labor. And sometimes we use prostaglandin analogs when abortion is mandatory.

5-Effect on respiratory system:

Aspirin has different effects on respiratory system according to the dose:

A-At **low doses** it will elevate blood CO2 levels, increasing the ventilation.

But why it increases ventilation?

Aspirin works as an energy-uncoupler. That interfere with oxidative phosphorylation process and that leads to more CO2 to be generated. This will stimulate our CNS , to increase the rate of ventilation.

Biochemical correlate :

Energy uncouplers : are certain chemical compounds that uncouples oxidation-reduction reactions in electron transport chain with ATP production , this occurs usually by creating alternative way for protons to diffuse along their concertation gradient other than ATP-Synthase.

The lost energy will be converted into thermal energy causing hyperthermia. Moreover ,low ATP levels will act as a negative feed back message to TCA cycle to run faster , producing more and more CO2

B-At **higher** doses it will act directly on our respiratory **centers , causing more and more hyperventilation leading to** respiratory alkalosis.

Contraindications:

1-Aspirin shouldn't be given to children below 12 years old who have viral infection . Because it may lead to Reye's syndrome.

Reye syndrome

Reye's syndrome is an extremely rare rapidly progressive encephalopathy which usually begins shortly after recovery from an acute viral illness, especially chickenpox and administration of

aspirin . It is a potentially fatal syndrome that has numerous detrimental effects on many organs, especially the brain and liver, as well as causing hyperammonemia and low blood sugar. The classic features are a rash, vomiting, and liver damage.

In these patients we have to look for an alternative drugs. Panadol or paracetamol used alternatively in patients with viral infection.

2- AROUND 50% of people have a hypersensitivity toward aspirin. Symptoms of sensitivity are like those of allergy :

A-**Edema**. Edema is a normal symptom for any allergic reaction. However , it may become more dangerous in the case of angioedema.

angioedema: is a rapid swelling in many tissues . Like mucosa , submucosa etc .. it may cause airways obstruction and suffocation

B-Anaphylactic shock, which is a serious allergic reaction that is rapid in onset and may cause death. It typically causes more than one of the following: an itchy rash, throat or tongue swelling, shortness of breath, vomiting, lightheadedness, and low blood pressure.

EPINPHRINE (adrenaline) is the primary treatment for anaphylaxis.

Pharmacokinetics

Metabolism occurs usually in the liver and it converts salicylate to a water-soluble form that will be excreted eventually through kidneys.

In patients who have liver problems, the dose must be monitored.

Doses

1. Aspirin as analgesic ….dose will be like 325 mg. (2 pills each day).
2. You should know that the protective use of aspirin will be at low doses like 81 or 80 mg. (baby aspirin) used as prophylactic from previous mentioned cardiovascular problems

3. We use it as anti-inflammatory just like in the case of rheumatoid arthritis (RA) we use much higher dose, in which we can use up to 12 or 20 pills per day to relieve the inflammatory condition associated with the disease.

- You just have to memories numbers mentioned in (Note 2 & 3).

Drug – drug interaction

- Aspirin is distributed in the body bound to a protein. Aspirin is known to displace a number of drugs from protein-binding sites in the blood, including the antidiabetic drugs tolbutamide and chlorpropamide, warfarin, methotrexate, phenytoin, probenecid. when it displaces warfarin for example, which is an anti-coagulant, the risk of bleeding will be elevated.

Sorry for any mistake. Please refer to slides.

Corrected and edited by Mohammad Qussay Al-Sabbagh