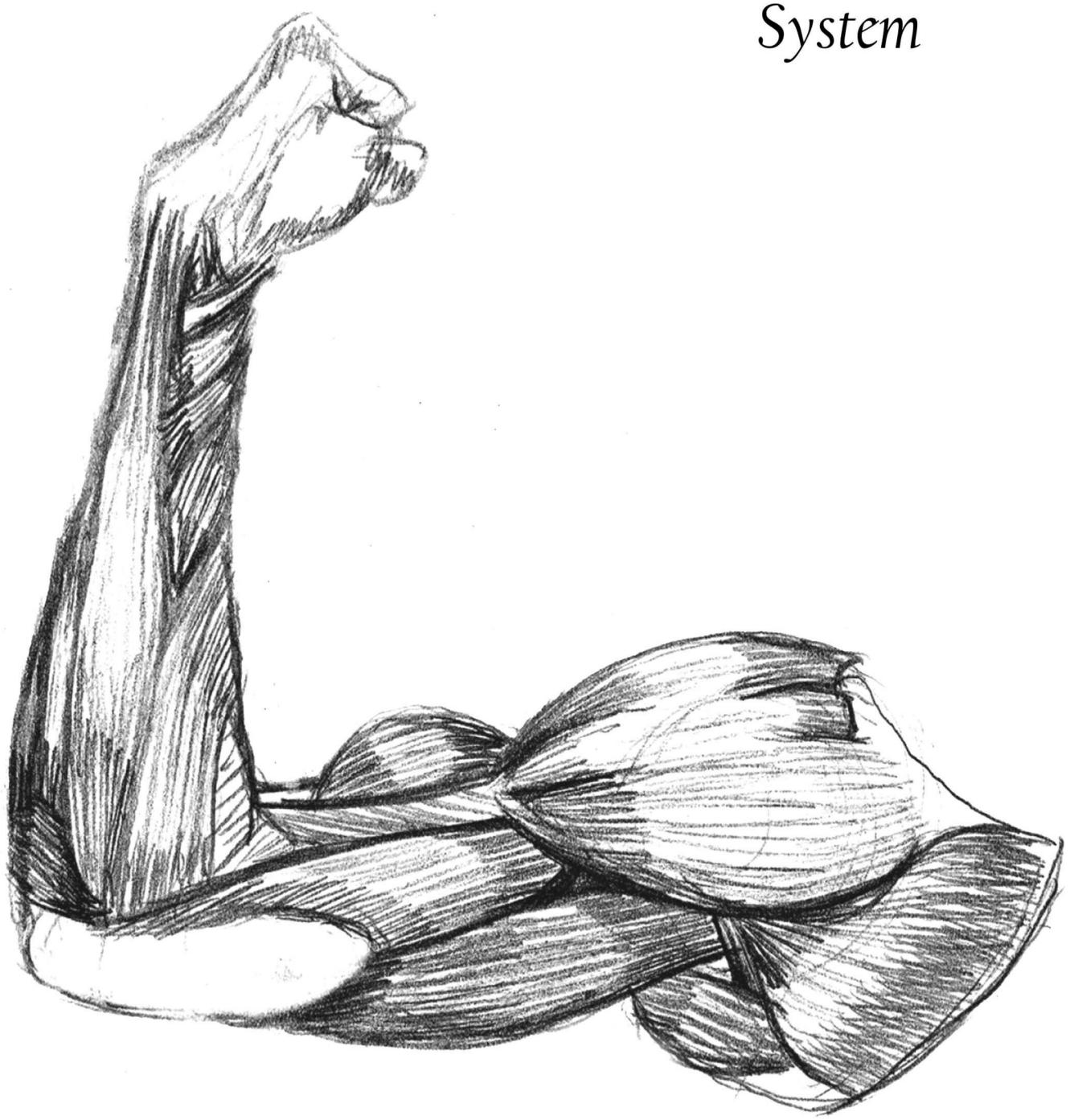
Medical Committee
The University of Jordan

The Skin and
MUSCULOSKELETAL
System



PHARMACOLOGY

SLIDES ☐
SHEET ■
LECTURE # **3**

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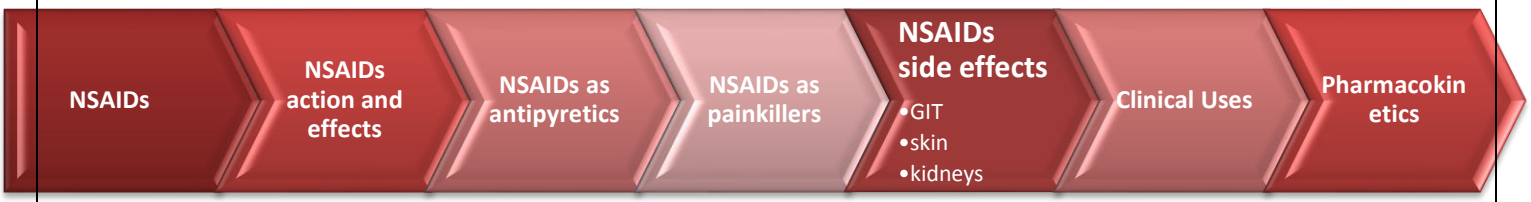
Anti-inflammatory Durgs



Anti-inflammatory Drugs

There are two groups of drugs for treatment of inflammation. The first one which we are concerned about is the **NSAIDs** (prostanoids), and the other one belongs to hormones-**glucocorticoids**. Corticosteroid hormonal drugs have corticols like cortisone.

But we are talking about NSAIDs that we are concerned about this lecture.

These drugs are group of drugs that are chemically not related, so what the relation between them?

Is that they have the same mechanism of action as prostaglandins synthesis inhibitors by inhibiting cyclooxygenase enzyme, so they inhibit this similar chemical structure in similar mechanism of action which leads to reduction in concentration of prostaglandins in tissues. So the result of the use of these drugs is indiscriminate decrease of prostaglandins concentration in tissues.

Effects

They inhibit COX enzymes which leads to decreased prostaglandin synthesis and thus decrease or inhibit the action of prostaglandin but with both beneficial and unwanted effects. As we know the prostaglandins are normal autacoids essential for *normal homeostasis* of tissues and the enzyme responsible for this process is *COX1*, they (the drugs) inhibit this enzyme indiscriminately and that will result in side effects. Also they inhibit *COX2* which is a *normal constituent of the cell*, but it is involved *specifically in the abnormal response of prostaglandins to injury, stress, inflammation or any pathological condition*. So when we use anti-inflammatory drugs,

we are mainly targeting this enzyme (COX2). But most of these drugs cannot differentiate between COX1 and COX2, so we'll get side effects.

We can understand this more by differentiating between the qualitative aspect of NSAIDs effects and quantitative aspects of the effects of these drugs.

- **Quantitative aspect:** they differ from each other in the *amount of inhibition* depending on the site of inhibition, the type of drug, the patient's age, genetics, pharmacokinetics, dose and many other factors.

To make things easier to understand and remember, we will put these drugs in groups and talk about common features, actions, side effects and mechanism of actions. Here are some common **characteristics:**

1- Share common pharmacological actions.
2- Most widely used drugs in the world in the treatment of rheumatic musculoskeletal diseases.
3- Most of them are OTC drugs; some few of them need to be prescribed by doctors. But put in your mind that even if they are OTC drugs that doesn't mean that they have no side effects.
4- None of them is ideal لوفي كان ارتحنا ...محدش كامل why we don't know. But part of it will be explained in the last lecture about the counter dose relationship.
5- Why we don't have ideal drugs that will help us, although they are about 50 types and 1000 preparations? Because they are different mediators, mediated by different enzymes and these mediators are inter-related with each other somehow. So they have different effects depending on dosing (large or small) like nitric oxide (small doses → inhibit, while large doses → stimulate).
6- Each patient may respond different from others.

What are the common actions?

* COX1 inhibitors: since COX1 is *normally* produced in normal individuals, when we inhibit it we will have side effects.

* COX2 inhibitors: we may have some side effects because it's a *normal* constituent of cells in the brain and bones. But it's the one responsible of the excess production of prostaglandins and responsible for the *pathology* inflammatory process, so if we inhibit COX2 we help the patient. However, if we inhibit COX1 we get side effects.

مرة سألني الدكتور في مقابلة الدكتوارة قبل شي 40 سنة أو أكثر، قلي شو الفرق بين ال pharmacology, physiology and biochemistry ؟ قلتله بال dose and route! –تصفير- قصة قصيرة!..

We have no ideal NSAID that can differentiate between COX1 &COX2, so they will be inhibited in ALL tissues.

***We inhibit COX2 in the pathological site → we get therapeutic effects.**

***We inhibit COX1→ we get side effects.**

Antipyretics

What is pyrexia? Fever. And what is fever? Hyperthermia, what is hyperthermia? It is elevation in the body temperature.

We have in the hypothalamus (small like hommos) in the brain, there is a thermostat in the hypothalamus like the heater in your house and you set it up on 70 degrees for example.

The normal body temperature is regulated by this thermostat in the hypothalamus. If you give NSAID to a normal individual nothing happens, the body temperature will not decrease. Agolkom sho kaman, in the slaicylate toxicity the body temperature increases and it is difficult to differentiate if the hyperthermia is due to drug toxicity or due to the original disease.

➢ What induces hyperthermia? Who is going to set and reset the temperature in your thermostat to an upper level?
Example is infection with bacteria. Infection causes release of toxins which lead to activation of WBCs and that lead to the release of **pyrogens.** Pyrogens go to the thermostat in hypothalamus, set it up and increase the body temperature.

How this normal thermostat keep normal body temperature mainly through cutaneous routes:

1- Vasodilatation
2- Increase respiration
3- Increase sweating. And so on.

So if you have a raised body temperature and you need to reset it and return it back to normal in the hypothalamus, this is what NSAIDs do. <u>They work on the hypothalamus and return the raised body temperature to the normal level.</u>

- **HOW**? By one of three ways, what we know until now is *prostaglandins COX2 inhibition in the hypothalamus*. But later you will know that this effect (inhibition in the hypothalamus) is induced by Paracetamol (AKA acetaminophen), and COX2 is elevated in rheumatic joints but Paracetamol has no effect on the joints, only on the hypothalamus. So why it inhibits COX2 of the hypothalamus and not the joints? Actually we don't know, maybe other mediators are present that Paracetamol can't inhibit. In the future we may know.

  Other possibility to explain this contradiction between paracetamol effects on hypothalamus and other tissues like stomach or joints is that sometimes we think that we have another COX enzyme called COX3 in the joints and it's not inhibited by Paracetamol.

****So there's no effect of NSAIDs on the normal body temperature. Because these agents essentially reset the "thermostat" toward normal. This rapidly lowers the body temperature of febrile patients by increasing <u>heat dissipation</u> as a result of peripheral vasodilation and sweating.**

❖ **Pain** (somatic/integumental pain), he will give us pain in CNS ☹
⇨ Analgesic effects (painkillers)مسكنات

We use it sometimes in pain and the mechanism you know about it; they work on prostaglandins. We use it to treat pain with inflammation; arthritis, bursitis, muscle pain or muscle ache, tissue injury, vascular pain, headache, arthralgia, myalgia, and dysmenorrheal and postpartum pain (after labor). As well as postoperative pain but NOT after grafts of the coronaries, it could be fatal (it is contraindicated in this case).

**Till now we don't know the mechanism of headache, but mostly because the vascularity in the meninges changes due to vasodilatation by some prostaglandins, so we inhibit this.

Further proved actions as **anti-inflammatory** drugs:

Initially it's a very complicated task. Why? Because there are so many mediators involved in this pathology (in the joint inflammation) not only prostaglandins. We have leukotrienes, histamine and prostacyclins. So if you are able to inhibit COX2, the others still work. Secondly, the interactions between these mediators, these mediators interact with each other when they're small doses, large doses and so on.

So we have no ideal drug in prostaglandins and no curative drugs actually. You can help them but no cure; you may help in pain, swelling, redness but not in the progress of pathology but you only can delay the process. That the most you can do.

In conclusion, NSAIDs mainly inhibit inflammatory and new response where COX2 action plays a significant role. What do we mean by that? We mean that if the pathology was due to mediators other than prostaglandins that are not COX related, we'll have no beneficial effect. They don't work on histamine or leukotrienes. However, if the pathology is due to increased COX2 activity and increase in prostaglandins, the patient will benefit from NSAIDs.

They have no effect on lysosomal enzymes, toxic radicals which kill the cells and cause arthritis, rheumatoid arthritis or vasculitis; all of them are not affected by NSAIDs.

The next common features of these drugs that **they have common side effects.** Since these drugs are commonly used by elderly people who are sensitive and weak because they probably have organ failures or diseases in liver or kidney, the side-effects are more common here.

We should inhibit the toxicity, I mean by this that intrinsic property of the drug itself. Because this property is particularly concerned with the intrinsic activity of that chemical molecules and its reaction in the body.

In Rheumatic fever we need to use NSAIDs in large doses for a long period of time. Elderly patients (risk patients) are particularly prone to side effects that can lead to death.

❖ Warnings:

Always found in the leaflets.

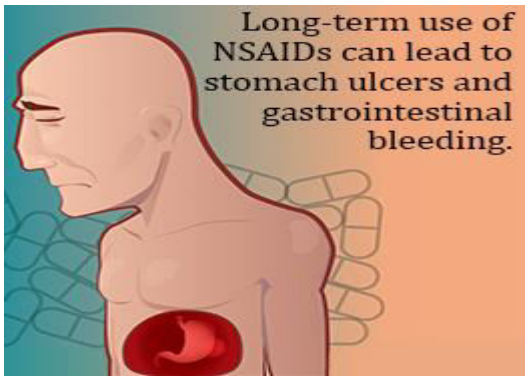
1- Cardiovascular system: thrombosis and Myocardial infarction and stroke shu bdk akthr mn hek, could be fatal.
2- These drugs are contraindicated in perioperative pain of coronary artery bypass graft/ surgery, we give them other drugs like morphine or Pethidine, but not non-steroidal because they are fatal for them.
3- GI tract: bleeding, ulceration, perforation in stomach and intestine and could be fatal, Especially in elderly عواجيز.

And this toxicity can happen at any time unfortunately without warning especially in elderly.

4- Elderly patients are at greater risk.

Aspirin is probably the only indication right now.

❖ **GIT side effects** are the most common in One out of five of patients especially in chronic users. Suddenly, with no warning (silent), the patient falls down due to gastric bleeding, ulceration and perforation, he may die before reaching the hospital.



You have to tell your patient that if he saw his feces black, that he has to go to doctor. And it's black (like tar) because acidity in the stomach turns it into methemoglobin which is black. Hemoptysis (coughing up blood) is due to bleeding from the lungs, while black tarry stool is from the stomach, and red stool is from the lower digestive tract (colon).

This is a piece of information from the internet and says all what the doctor wants to say. ((Black stool that is tarry in texture and foul smelling is often a symptom of upper gastrointestinal bleeding from the esophagus, stomach or small intestine. This is called melena. Rectal bleeding of bright red blood with clots, sometimes mixed with stool, is called hematochezia. Hematochezia is often caused by bleeding from the lower digestive tract, including the colon, rectum or anus.))

These are serious side effects.

Mechanism of action of COX1 inhibition

These side effects are due to inhibition of COX1 in stomach in the pylorus particularly, because prostaglandin E2 is involved in keeping the normal homeostasis of parietal cells. What's the function of PGE2?

1- To maintain the normal homeostasis.
2- Keep mucous secretions and protecting layer.
3- It provides feedback inhibition of HCl secretion from the fundus. So PGE2 is released from pylorus and when acid increases, as a feedback inhibition it goes to the parietal cells in the fundus (which secrete the HCl) and stops secreting it and decreases HCL production.

By these mechanisms PGE2 protects the stomach.

What will happen if you inhibit it? There will be a decrease in PGE2 levels and inhibition for the secretion of mucus and inhibition of the feedback inhibition of HCL production, so you get hyperacidity and injury to cells and protective layer.

What will happen then? Digestion of the wall of the stomach and protective layers including blood vessels, so we'll have ulceration and perforation.

In this case, especially with salicylate, what complicates this process? Having antiplatelet effect because salicylate inhibits COX1 in platelets, so hemorrhage/bleeding continues and within no time the patient will develop anemia.

Signs and Symptoms.

For elderly can be **asymptomatic** -silent- so if they were ill there should be someone around them to take care of them. Might be symptomatic like:

1- Dyspepsia النفاخ: a generic term for mild disorders of digestion, characterized by stomach pain, discomfort, heartburn and nausea, often following a meal ((from internet: it is a medical condition characterized by chronic or recurrent pain in the upper abdomen, upper abdominal fullness and feeling full earlier than expected when eating))
2- Diarrhea. اسهال
3- Sometimes constipation (rarely).
4- Nausea and vomiting.
5- Gastric bleeding, Ulceration and Perforation.

From the book: ((Gastrointestinal: The most common adverse effects of NSAIDs are GI related, ranging from dyspepsia to bleeding. Normally, production of prostacyclin (PGI2) inhibits gastric acid secretion, and PGE2 and PGF2α stimulate synthesis of protective mucus in both the stomach and small intestine. Agents that inhibit COX-1 reduce beneficial levels of these prostaglandins, resulting in increased gastric acid secretion, diminished mucus protection, and increased risk for GI bleeding and ulceration. Agents with a higher relative selectivity for COX-1 may have a higher risk for GI events compared to those with a lower relative selectivity for COX-1 (that is, higher COX-2 selectivity). NSAIDs should be taken with food or fluids to diminish GI upset. If NSAIDs are used in patients with a high

risk for GI events, proton pump inhibitors or misoprostol should be used concomitantly to prevent NSAID-induced ulcers.))

❖ **Skin effects** are the second most common after GI effects. Most are mild but they can rarely be life-threatening. 10-15% of cases of tiaprofenic acid derivatives, 5-10% cases of sun black (it's not clear in the record) , rashes of different types, urticaria, photosensitivity when patient is exposed to UV rays which causes redness and melasma sometimes, especially in chronic use, and it's rarely fatal.

❖ **Kidneys (Adrenal) side effects** either acute or chronic.

- Acute: due to kidney injury in the tubules, you can notice that the urine is turbid, and if you test the blood you will see raised **creatinine** levels.
  - You have to pick the patient very early, why? Because these effects are reversible. If you stop the use of the drug, the patient will return back to normal. These side effects do not happen in normal patients with normal renal function, but you have to be careful when using these drugs with patients who have compromised renal functions, renal failure or insufficiency.
  - So you have to always monitor the urine and the level of creatinine. If anything happens we have to stop these drugs.
  - Don't use them with other nephrotoxic drugs.

- Chronic: prolonged use of these drugs in elderly or renal insufficient patients. It affects the normal homeostasis of the blood which is controlled by adrenaline and angiotensin II that make constriction of post-capillary venules. These drugs inhibit this process which results in renal insufficiency.

From the book: ((Actions on the kidney: NSAIDs prevent the synthesis of PGE2 and PGI2, prostaglandins that are responsible for maintaining renal blood flow. Decreased synthesis of prostaglandins can result in retention of sodium and water and may cause **edema** in some patients. Patients with a history of heart failure or kidney disease are at particularly high risk. These effects can also mitigate the beneficial effects of antihypertensive medications.))

So many people we know take these drugs as habit; warn them not to do that.

LAST SLIDE!

Common clinical use:

1- Analgesics: simple integumental superficial pain, for example headache, dysmenorrhea, back pain, bone metastasis with analgesics "increase the dose", post-operative pain, and tooth ache if not contraindicated but doesn't work with severe pain like bone fracture or deep pain like in angina and burn.
   - Short term therapy: drug of choice → aspirin, paracetamol and ibuprofen
   - Long term therapy: Diflunisal, Naproxen and Piroxicam
2- Anti-inflammatory
3- Antipyretics

*** Pharmacokinetics:** These analgesics undergo **quantal** dose response relationship. They are either effective or not effective at all regardless to the dose given. Patients either respond or don't respond, how do we know? We don't have tests to know that, so by error and trial. You tell your patient to try this drug, if he relief → he continues otherwise you ask him to come back to you.

These drugs follow first order kinetics; their elimination depends on the half-life not the dose.

In zero order kinetics there's saturation of the enzyme, but dose response relation it's the relation between the drug and its effect (response). If the drug follows the sigmoidal dose response relationship → if you increase the dose, the effect will increase. But in quantal dose response, the patient either responds or not like some antipyretics and some analgesics.

- I'm sorry for this horrible sheet, but I couldn't make it any better. Good luck! ☺

Dedications goes to 5C :P