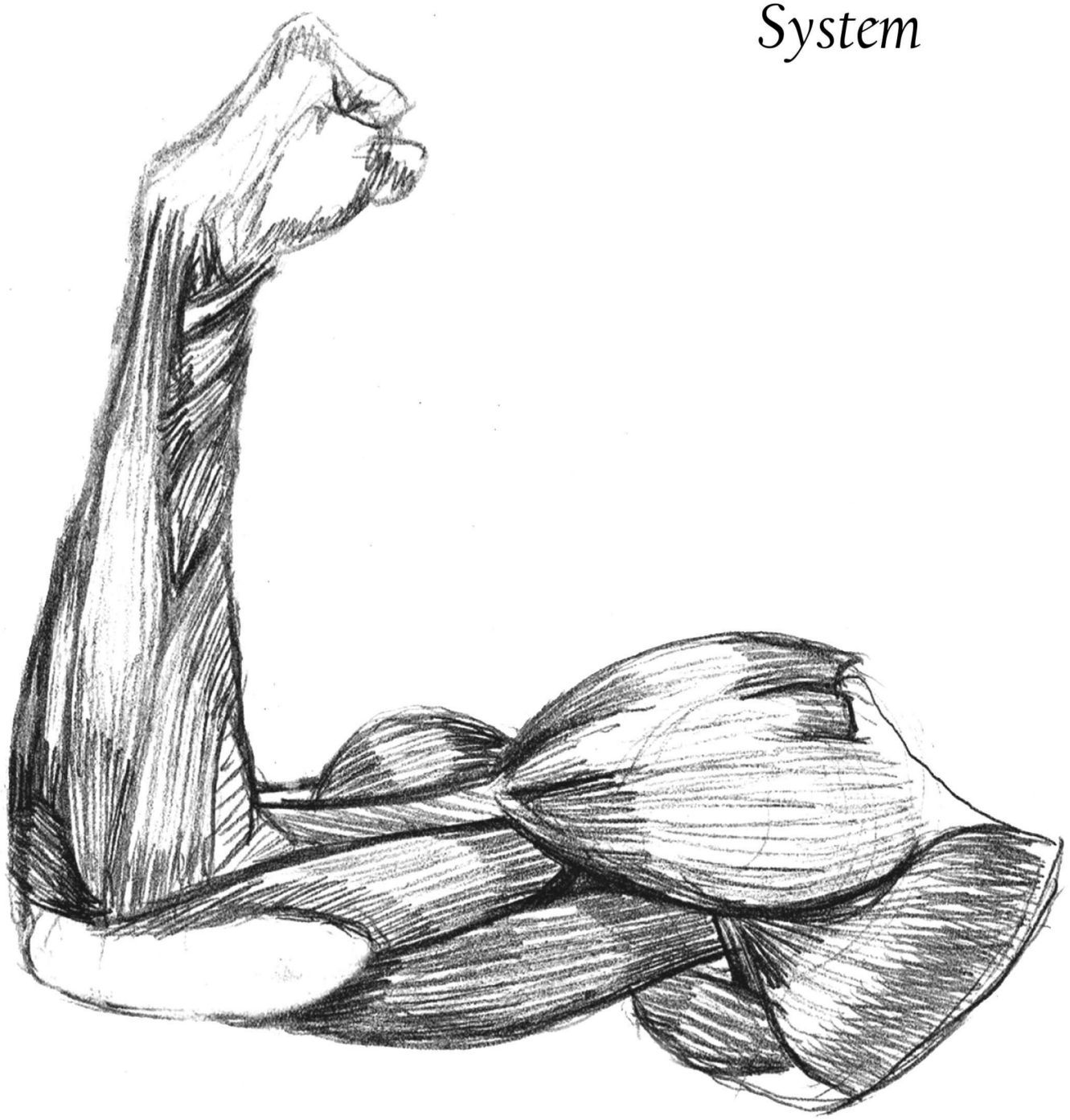
Medical Committee
The University of Jordan

The Skin and
MUSCULOSKELETAL
System



PHARMACOLOGY

SLIDES ☐
SHEET ■
LECTURE # 4

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Aspirin as NSAID

- Anti-inflammatory drugs:

1. **Aspirin**:

- The most commonly used drug.

- It's on OTC drug, it's not always prescribed by doctors and that increases its risks unless the patient took care while using it.

- Known as **AcetylSalicylic Acid (ASA)**.

- It's an old drug, it was first synthesized by Bayer Company in Germany in 1885 from the bark of the salicylate plant, and then it became synthetic also in 1937 aspirin become used in USA after the FDA had approved it.

- Aspirin was the trade name, now it the generic name.

- Often anti-inflammatory drugs are compared to aspirin in drug trials (that's mean that aspirin is main drug in clinical use).

(Please note that in drug trials, the new drug should meet 2 criteria: Safety and efficacy).

- It's relatively insoluble.

2. **Sodium and Calcium salts**:

- They are available.

- Readily soluble drugs.

- Their solubility is important for drug absorption.

3. **Difunisal:**

- It's relatively a new drug.

- It's related to Salicylate (not salicylate) but its better because it causes less GIT irritation than aspirin and relatively more soluble.

- It's a long acting drug.

(You should know that the toxicity of salicylate is very serious, it's called Salicylism, BUT in Difunisal even the toxic dose doesn't produce Salicylism)

Pharmacokinetics of Aspirin:

It is important to know the drug forms, as we have different forms of drugs: one for Oral administration, one for topical applications

The **Oral** form has different dose forms: some are tablets; these tablets can be simple or coated to be resistant to the acidic medium and to dissolve in the alkaline medium to decrease irritability of the gastric mucosa, another form for oral administration is the powder form.

When we talk about Pharmacokinetics, we talk mainly about four items:

1. Absorption
2. Distribution
3. Metabolism
4. Excretion

1. Absorption:

We absorb drugs by one of three routes either by Oral administration, Rectal/anal administration or by Skin.

- After Oral administration, you have to consider the Rate of Absorption and the Extent of Absorption.

Concerning the RATE of Absorption:

- Aspirin is a weak organic acid.

We took before that passive absorption depends on whether the drug is ionized or unionized in the gastric juice.

☒ The ionized form can't be absorbed while the unionized can be easily absorbed.

- So since Aspirin is a weak organic acid in and acidic medium in stomach, it will be present as Unionized form.

❖ So the RATE of absorption in *stomach* is HIGH and higher than the rate of absorption in the small intestines.

What about dissolution?

- Any drug should be in a soluble form to be dissolved.
- Rate of dissolution is important for absorption.
- So since Aspirin is a weak organic acid, it's most likely to be DISSOLVED in Alkaline medium in small intestines (in ileum or jejunum).

☒ In alkaline medium, the percentage of the unionized form is lower than in stomach indicating that the ionized form is higher in the small intestines.

❖ So the RATE of absorption in *small intestines* is LESS, but the **Extent** of absorption is **High**.

Most of anti-inflammatory drugs are absorbed from the ileum and jejunum, although the Rate of absorption is higher in stomach, WHY?

✓ Because of the surface area.

☒ The surface area of stomach is 1 square meter, while the surface area of ileum and jejunum is 6 square meter, WHY?

✓ Because of Microvilli.

- Rectal Absorption

- Is erratic (random and irregular)
- Rectum is not an area for absorption, but sometimes we are obliged to administer drug through this route in exceptional cases such as: vomiting, unconscious patients and the weak elderly patients.

- From Skin

- Methylsalicylate is used locally and get absorbed systematically.
- Absorption is not readily as from the GIT.

2. Distribution:

- Aspirin is highly bound to plasma proteins in the acidic "non-specific" binding sites on albumin, 90-95 % is bound and this characteristic that makes this drug suitable for drug-drug interaction in this site.

- The site of action as antipyretic is at the hypothalamus, that's why this drug has to pass the blood-brain barrier; so Aspirin can but Difunisal cannot pass.

  - ❖ So Difunisal cannot be used as ANTIPYRETIC.

- It can pass through Placenta and reach the baby and it may lead to drug-drug interaction.

  - ❖ So Aspirin is contra-indicated for women in their third trimester and during labor as it may lead to hemorrhage beside its pharmacological action.

3. Metabolism:

- Could happen in tissues, plasma and blood.

- In tissues: Mainly the liver. It will become active (Salicylte) by the action of esterase enzyme, that's why it must be in deacylated form before it can be active because the acetyl group is the group that is active.

- For elimination, the drug can go through Oxidation or Conjugation with glucoronide or sulfate in liver and the water-soluble metabolites will be eliminated through the urine.

4. Excretion:

- Mainly in urine

- In lactating women, it can be excreted with milk (here we should care about the baby she is feeding)

- In cases of Toxicity, we need to get rid of the drug, how?

☒ Since the drug is in the urine, you can enhance excretion by making the drug in the urine more ionized because it's a weak organic acid and you want to inhibit reabsorption and increase elimination.

❖ You can inhibit reabsorption by alkalization of urine and this is done by using **BICARBONATE**.

- Since 95% of Aspirin is bound to plasma proteins, these proteins can't pass glomerular filtration because they are large molecules, and the drug bound to the protein can't pass either. So the major route of elimination of drug is by active secretion.

☒ (You should know that for active elimination through the nephron in the kidney, we have 2 major routes 1 for basic drugs and the other for acidic drugs. So basic drugs compete with each other on the basic route of elimination as the acidic drugs compete on the acidic route)

- NOW, Uric acid, which is an endogenous substance of Purine catabolism of RNA and DNA, and Salicylic acid are weak acids so they compete.
  But you have to know that in small doses, this drug causes gouty attacks due to inhibition of uric acid excretion at proximal nephritic tubules. In large doses, Aspirin act as a uricosuric drug – increasing the excretion of Uric Acid – This action takes place in the distal convulated tubules.

So Aspirin compete for reabsorption against uric acid and the net effect (The balance between the effect on the proximal tubules and the distal tubules) is the elimination of Uric Acid.

- ❖ Aspirin in small doses ==➔ Precipitate uric acid causing gouty attacks.
- ❖ Aspirin in large doses ==➔ Used to treat Gout.

- Aspirin should be avoided in patients with renal and liver diseases.

Half life and Clearance of drugs :

- Aspirin in small doses follow first order kinetics which means that the elimination is in linear relation with the dose. So it's dose independent.
  - ☒ It's half life almost 3.5 hours
- In large doses, it follows Zero order kinetics, which means that the enzymes of glucuronidation and oxidation in the liver at a certain level will be saturable. So at certain level no more metabolism of this drug, no elimination, so it accumulates.
  - ☒ That's why you should take care during drug prescription by do kidney and liver function monitoring, Because If you increase the dose by small amount , you'll get huge increase in drug concentration and toxicity and Vice versa, If you reduce the dose by small amount , you'll have the sub-therapeutic levels.

The effect on CycloOxygenase Enzyme:

- Due to binding of Salicylate on the binding site of COX enzyme, which is Irreversible, Meaning once Salicylate is bound to the platelet it inhibit its function permanently.
  (Note that 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)

- ☒ If the patient got acute hemorrhage and severe bleeding, I should immediately stop using the drug, But its effect will not stop, What should I do? Give him fresh blood/plasma (containing functional platelets)
- ☒ But if I want to perform a surgery and the patient has took Aspirin , I should tell him to get back after a week – 10 days (Half life of platelets) to prevent bleeding during surgery.

Mechanism of Action:

- Aspirin blocks synthesis of Prostaglandins at peripheral tissues e.g. Skin
- Works as Antipyretic , produce sweating and vasodilatation
- decrease sensitivity of pain receptors
- But it doesn't work on the Cortex, so it doesn't work on pain centers at the parietal lobe (postcentral gyrus), whereas Morphine does.
- It inhibit pain stimuli at subcortical levels, e.g. Hypothelamus(as anti-pyretic) , thalamus and spinal cord(as analgesic).
  - ☒ In hypothalamus, it works on COX1 or COX3 or as acetaminophen in unknown mechanism.
- Acetylsalicylate inhibits both COX1 and COX2.

Pharmacological Action:

- The three major therapeutic effects of all NSAIDs are: Anti-inflammatory, Anti-pyretic and analgesic effects.
- Nowadays, Aspirin is most commonly used (and it's the only one) in cardiovascular diseases because it works on platelets.
  - ☒ All the other NSAIDs are contraindicated.
  - ☒ Aspirin decrease in elderly the cardiovascular accidents, but it should be used in small doses as Anti-platelet.
- 50% of people taking Acetylsalicylate in small doses continuously, incidence of Colon and Rectum cancer are less.
- Useful in Alzahaimars disease.

- Its Toxicity can cause HYPERTHERMIA and it will be hard for doctors and parents to determine whether hyperthermia is from the original disease or from its toxicity, so doctors should do blood level monitoring and see the real cause.
  - Above 50mg/dL ➔ Toxicity
    - ☒ WHY Hyperthermia?
    - ✓ Due to uncoupled oxidative phosphorylation. We know that energy in our bodies is stored as ATP but Salicylic acid inhibits this process, So energy will be dissipated as heat instead of being stored as ATP, and the body's temperature will increase.
- Respiratory reactions: It causes hyperthermia, hyperventilation, respiratory associated depression, respiratory central atresia and hepatotoxicity in abdomen (please refer to the record of sec 1 at 32.07 min).
- **GIT:**
  - ☒ normally prostaglandins increase mucus secretions which is important to protect the mucus membranes, and feedback inhibition of HCL secretion
  - ☒ If Aspirin inhibits this process, HCL will increase and mucus secretion decrease.. **As** a result microhemorrhage , ulceration and perforation of the mucosa might occur, If it(the acid) reached the blood vessels severe and unstoppable (remember antiplatelet action)bleeding might happen leading to anemia and in this cause surgery is needed to stop the bleeding.
- **Cardiovascular system:** Effect on platelets
  - ☒ **Low** dose = 60-80 mg , High dose = 4 g (in rheumatism)
  - ☒ **Irreversible**
  - ☒ It can cause bleeding, as it inhibits prostaglandins and affect the clotting time and coagulation which is not only caused by its effect on platelets also the effect of drug on the endothelial cells of blood vessels by inhibiting Prostaglandins synthesis in these sites.
- **Effect on kidney :**
  - ☒ This drug may lead to kidney toxicity in the following diseases : liver diseases , kidney diseases and heart diseases

☒ When diuretics are taken, blood volume or renal blood flow is decreased, stimulating constrictors e.g. Catecholamine and Angiotensin 2, which cause vasoconstriction. Such a process is opposed by prostaglandins to maintain normal blood homeostasis in the kidney. BUT WHEN YOU TAKE ASPIRIN, IT WILL INHIBIT PROSTAGLANDINS and this process won't be opposed, vasoconstriction will happen, renal blood flow will decrease leading to kidney diseases.

THERAPUETIC USES :

☒ Used as Anti-inflammatory , antipyretic and analgesic in the following diseases : - Rheumatic fever – Rheumatic arthritis – Osteoarthritis – Myaglia – Arthralgia

✓ Doses :

As an analgesic give it in Small doses.

As an Anti-inflammatory give it in large doses.

☒ The most important use is in GOUT , as an uricosuric agent (when used in large doses) as small doses do the opposite.

☒ In cardiovascular: it's Anti-platelet.

☒ Decrease the incidence of colon and rectal cancer.

☒ In Alzahaimers disease.

☒ Used to prevent radiation-induced diarrhea.

SIDE EFFECTS:

- In GIT: epigastric distress, nausea, vomiting, microscopical bleeding, ulceration, perforation and bleeding.
- In blood: bleeding, irreversible binding and drug-drug interaction.
- In respiration : large toxic doses inhibit the respiratory center , it may lead to death
- Metabolic reactions: large doses lead to uncoupled oxidative phosphorylation leading to HYPERthermia.

- Hypersensitivity: happen in 15%, May induce rashes, urticaria (حكة), edema bronchoconstriction and anaphylactic shock (very dangerous could be fatal but it is rare).

Toxicity :

- Metabolic changes might be mild, severe or lethal. It happens in children more than adults
- Once Toxicity happens it's an emergency situation (the patient should go to the hospital).

☒ Mild intoxication (50 mg/dL) = salicylism

Characteristics: - nausea – vomiting – hyperventilation – alkalosis – headache – mental confusion – dizziness

☒ Severe intoxication :

- Initially, stimulation of the CNS happens causing: restlessness, delirium, hallucination and convulsions.

- Then: - Depression of RC – Retention of CO2 – Increase plasma CO2- Decrease plasma Bicarbonate – Respiratory acidosis.

☒ Fatal/lethal intoxication :

- Vasomotor collapse, coma, dehydration, respiratory failure, metabolic acidosis and finally DEATH.

TREATMENT :

- Mild intoxication : by treating the symptoms
- Severe intoxication: patient should enter the hospital and be treated and given IV fluids and do alkalization of urine.

Drug-drug interaction:

- It is important because aspirin is **OTC** drug so when you ask your patient about the drugs that he is taking, he may forget to tell you about it so make sure to know all the drugs that is taken by your patient.
- Because it's highly bound to plasma proteins, it can displace other narrow therapeutic drugs like Warfarin (which is 99% bound), If it displaced Warfarin and this will lead to raise the free (not bound) percentage of the drug to 2% which was originally 1% , Warfarin will cause hemorrhage as it works on blood.
  (In treatment of thrombosis, we give the patient Heparin in the hospital, when he goes home you'll give him Warfarin . Here you should warn your patient about this important drug-drug interaction and change the dose if he's taking Aspirin or bleeding might occur)
- In chronic administration, this drug is contraindicated with probenecid and sulfinpyrazone , especially in blood.

PREGNANCY :

(The FDA categorized drugs to A,B,C,D)

- During the first and second trimester , Aspirin is considered as Category C (should be given on in serious cases with good monitoring of kidney and liver function because it's very dangerous)
- During the late trimester, it's considered as category D (NEVER use it, it will lead to hemorrhage.
- In lactating women, it will be secreted with milk and it might harm the baby.

Sorry for any mistakes.

Good Luck =)