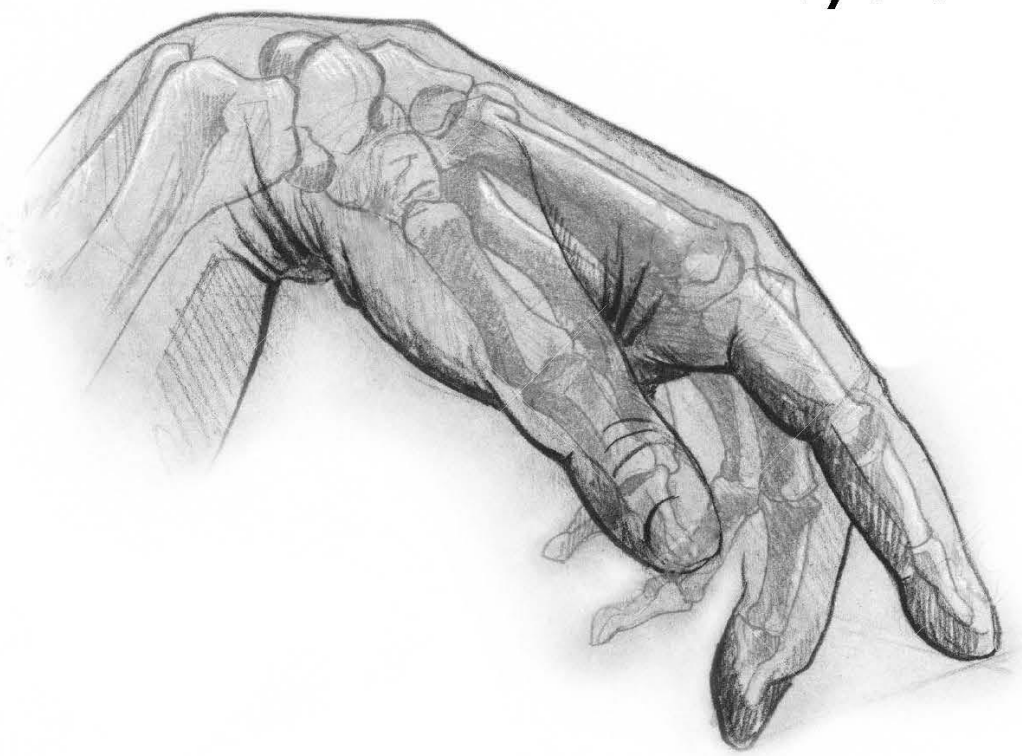
The

Musculoskeletal

System



Pharmacology

☑ Sheet ☐ Slide ☐ Handout

Number:	1
Subject:	NSAID
Done By:	Bushra Arafa Zayed
Corrected By:	Hashim A. Mohammad
Doctor:	Alia' Shatnawi

Date:

Price:

- Topics of this lecture:
  - Revision
  - Anti-inflammatory drugs (aspirin)

NOTE: The sheet was written in an order that differs from the record to make things more clear

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Remember: not the entire ingested drug is absorbed (certain percentage only)

❖REVISION :

The doctor at the beginning reminded us with somegeneral information:

- **Antibiotics:** drugs that kill microorganisms
- **Pharmacokinetics** : how the body deals with drugs.
  - Pharmacokinetics phases:
  1. Absorption
  2. Distribution: through the blood to reach different parts of the body.
  3. Metabolism:
     Remember: First pass effect → the effect of the liver on the drug after reaching it from the portal circulationbefore reaching the systemic circulation.And usually it causes inactivation of the drug, and thus decreasing the bioavailability.
     - The purpose of metabolism is to :
       - Convert the active drug to an inactive form (the liver thinks of everything as a xenobiotic, so it tries to get rid of it).
       - Convert the drug into a more soluble form that can be easily excreted through the kidney. [Conjugation with glucuronic acid provides –OH groups, increasing the solubility, and facilitating excretion).
     - If we have a drug with a high first pass effect, in order to achieve the desired concentration in the blood (i.e. to produce the intended effect) we:
     - -Give higher doses of the drug orally
     - -Or we give it IV, to avoid the first pass effect.
  4. Execration.

NOTE: we should remember these things as we will talk about them for each drug.

- **Pharmacodynamics:** How the drug affectsthe body.
- Most of the drugs work on receptors as targets (eitheras agonists or as antagonists), and once they are bonded to the receptor, the effect is produced. ”from here it is all about dynamics“

NOTES ABOUT THE COURSE GENERALLY:

From now on, we will learnsystemic pharmacology, starting with the MSS.

What we should know about each drug:

- The intended use of the drug (why do we use it).
- The pharmacological form (i.e. the route of administration: tablet, injection…..).
- Side effects.
- The mechanism of action of each drug (we will know from its mechanism the pharmacological effect and the side effects).
- The doses are not required from us unless where we are told so.
- Drug-drug interaction: how drugs interact with each other during the different phases of the pharmacokinetics and dynamics as well.

NOTE: the doctor said that she will not focus on thenumbers; it is all about the things how it go rather than numbers.

- In this course we will talk about six topics:

1-Anti –inflammatory drugs:including,the non-steroidal and those used to treat rheumatoid arthritis (RA).
2-Drugs used for gout disease.
3-Skeletal muscles relaxants.
4-Skin pharmacology: drugs for skin diseases and the drugs that are used topically but not to treat skin it self.
5- Leishmaniasis and leprosy which are old diseases although we will talk about them in brief.

This sheet will cover the **non-steroidal anti-inflammatory drugs (NSAID)**

❖Non-steroidal anti-inflammatory drugs(NSAID):

- Remember: inflammation is the response of the body against an invading microorganism. And after a while, this response should stop OR it will turn into a chronic inflammation. In other words, we need to get rid of the invading agent and then to get rid of the inflammation.
- The inflammation has some signs: pain, fever, itching and swelling…
- The purpose of the anti-inflammatory drugs, in general, is to stop these signs either caused by infection or by an auto-immune disease (like the inflammatory bowel disease or rheumatoid arthritis) as if it continues it's going to lead toa damage.
- Auto-immune diseases happen when our immune system recognizes a normal antigen in the body as a foreign one and attacks it causing inflammation and damage. Like in RA where we have rheumatoid factor and it causes swelling of the joint, redness and pain leading to damage in the joint and may cause disability to the patient.
- **Non-steroidal anti-inflammatory drugs:** are drugs that have anti-inflammatory properties but they are not from the family of steroids.
- NOTE: the **steroidal-anti-inflammatory drugs** are corticosteroids like the cortisone. Theyreduce the inflammatory responses in the body (we will take it in the endocrine system).

We will start with the first drug **<u>Aspirin</u>**

• Aspirin

- Its chemical formula is acetylsalicylic acid. It is a synthetic form of salicylate.
- It is a historical drug that was extracted from the Bark of WillowTree (salicylate) لحاء شجرة الصفصاف, they used to put it on wounds.
- In general, it is used to prevent the recurrence of a stroke or myocardial infarction byreducing the platelets activity.
- Also used as anti-inflammatory drug.
- Now to understand the effects of aspirin we will talk about the pathway that it works on which is the cyclooxygenases pathway.

<u>Normally:</u>

- The pathway is activated when we need a response to a certain stimuli ⟶activation of phospholipase A (PL-A) that

Remember: pain is caused by the chemical mediators secreted by cells like interleukins and cytokines.

cleaves phospholipids of the cell membrane producing arachidonic acid→→arachidonic acid enters one of the two pathways :1-cyclooxygenase pathway or 2- lipooxygenase pathway(both of them are involved inflammation)
-the cyclooxygenase pathway results in the formation of different kinds prostaglandins like PG E,D,I and thromboxane A2.

NOTE: Prostaglandins are not considered as hormones, because they act locally (i.e. autocrine or paracrine function).

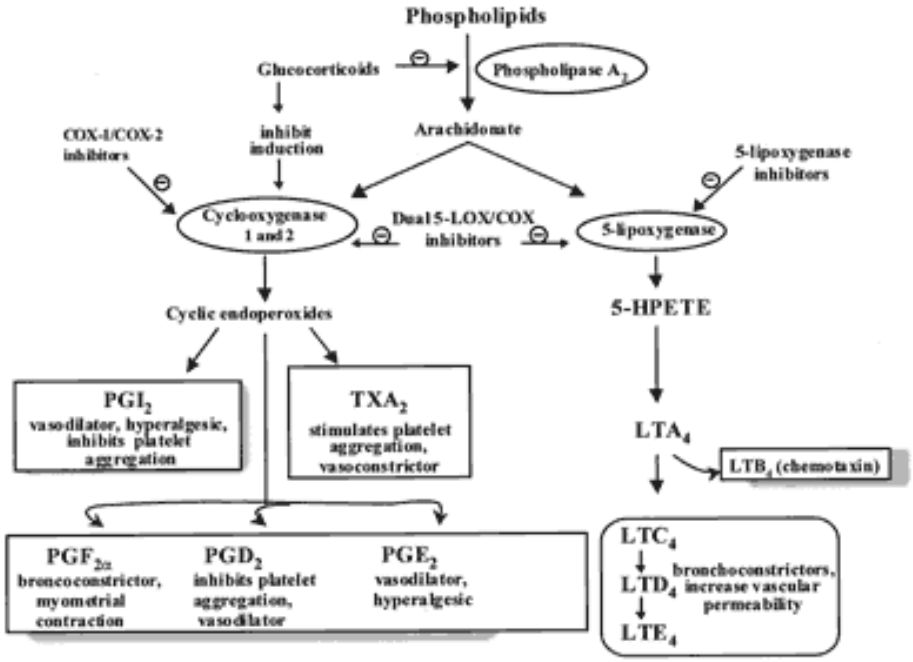
- Prostaglandins have many effects such as pain, dilation of blood vessels(smooth muscles relaxation in the vessel), bronchoconstriction,increase secretion and also activation of more and more leukocytes leading to more inflammation.

- NOTE: The enzyme cyclooxygenase has two isoforms COX1 and COX2..

- The difference between both isoforms: firstly, the location, where each of them is expressed. Secondly, the way they are stimulated. CoX1 is stimulated all the time and it is present mainly in the stomach, intestine, kidneys, platelets, endothelium and other places. While COX2 is an inducible form and found in inflammatory cells. So COX2 is stimulated during inflammation only not all the time.

- NOTE: each prostaglandin has different effects on different tissues, some cause blood vessels dilation (Relaxation of smooth muscle) and at the same time they cause contraction of the uterus so they may be used to induce labor.
- <u>More specifically,</u>
  1. **Prostacyclin**(PGI2): is one kind of prostaglandins and it is the one responsible for vasodilatation(the doctor said that this one is important).
  2. **Prostaglandins E** causes vasoconstriction.
  3. **Thromboxane A2 (TX A2)** causes platelet aggregation that leads to blood clotting.

- So simply non-steroidal-anti-inflammatory drugs in general and **ASPIRIN** specifically inhibit cyclooxygenase pathway inhibiting both isoforms COX1 and COX2 (although it might have more preference to inhibit COX1 but usually we see the effects of inhibiting both of the isoforms)….inhibiting the formation of prostaglandins of all kinds: the ones that cause the inflammatory response that's why it is an **anti-inflammatory drug** as well as the TX-A2 preventingplateletaggregation and blood clotting and this is why it is used as **anti-coagulant**مميع للدمreducing the risk of the stroke and myocardial infarction.



- Anti-inflammatory drugs **sometimes**are usedto reduce the symptoms of **asthma** as they prevent the bronchoconstriction by inhibiting the synthesis of prostaglandins. But the lipooxygenase pathway inhibitors are more commonly used in asthma as they affect the inflammatory response in asthma in a more direct way.

- In addition to the effects of the prostaglandins we mentioned, they have protective effects on the stomach and inhibit acid secretion (this is the effect of COX1 specifically). So inhibiting the production of the prostaglandins by Aspirin will increase the acid secretion in the stomach and damage the protective layer on the wall of the stomach causing peptic ulcer and irritation.
- **So the side effect of the Aspirin is peptic ulcer and irritation in the stomach.**
- That's why Aspirin should not be taken on an empty stomach and also the non-steroidal anti-inflammatory drugs in general.
- Aspirin is contraindicated in peptic ulcer patients to avoid bleeding.
- In other words, the side effects of aspirin are associated with inhibiting COX1 and the anti-inflammatory effects are associated with COX2 inhibition.
- Scientists tried to make drugs to inhibit COX2 only to overcome the side effects of the non-steroidal anti-inflammatory drugs as COX2 is not found in the stomach.
- NOTE: ibuprofen, diclofenac-sodium(voltaren) and diclophinic-potassuimare allnon-steroidal anti-inflammatory drugs.

peptic ulcer: is a discontinuation of the layer that lines the stomach

- Also these drugs are used as analgesics (pain killers).
- the non-steroidal anti-inflammatory drugs are used as:

1. Anti-inflammatory.
2. Analgesics (means without-pain).
3. Antipyretic خافض للحرارة.

- **Lipooxygenase pathway:**
- The lipooxygenase pathway also works on arachidonic acid converting it to **leukotrienes**(B, C, D, and E) which are involved in inflammation, also increase vascularpermeability, increase secretion,bronchoconstriction and they activate phagocytes system.
- But this pathway is not inhibited by the non-steroidal anti-inflammatory drugs. It is inhibited by lipooxygenase inhibitors such as zileuton which is used to treat asthma.
- Also we have a group of drugs that inhibit the effect of leukotrienes by working as antagonists on leukotrienes receptors (not by inhibiting the pathway itself) and they are also used to treat asthma such as montelukast.
- NOTE about gout: it is an inflammation caused by uric acid crystals deposited in the joint. The inflammatory response is to get rid of these crystals.One of the drugs used in gout colchicinethat prevents microtubules formation which are needed in leukocytes in order to engulf materials or move.So colchicine inhibits this process, decreasing the inflammatory response. The doctor said that this drug may be used in the future in treating cancer as it inhibits the microtubulesformation which are formed during the cell division to separate chromosomes from each other.

  - Colchicine acts in a similar mechanism to some chemotherapeutic agents used in cancer, that's why it can be used in cancer.
  - The corticosteroids inhibit the first step of the pathway. They inhibit the enzyme phospholipase A, preventing the formation of all arachidonic acid metabolites.

❖ non-steroidal inflammatory drugs as analgesics VS opioids

Opioids (narcotics)	**non-steroidal inflammatory drugs**
Morphine	Aspirin
Work on CNS so relief any kind of pain	Work on the peripheral nervous system (on MSS),decrease nociception of pain
Inhibit pain receptors in the brain (antagonists)	COX inhibitors
Very strong (used in a very strong pain)	Weak (they are used in case of weak to moderate pain)
The repetitive use causes tolerance that leads to addiction(so only given with prescription)	Peptic ulcer
Don't affect the inflammatory system or the immune system in general so they are neither antipyretics nor anti-inflammatory. ONLY analgesics	They areAntipyretics, analgesics and Anti-inflammatory

- Note: Paracetamol is not a non-steroidal inflammatory drug but it is grouped here as it has similar effects.
- The doctor mentioned some notes about pain :

-Pain is the main cause why people come to doctors.

-Pain has many types:

1. Sharp (like when the skin is injured by a knife)
2. Nagging (toothache)
3. Dull
4. Throbbing
5. Boring
6. Stabbing
7. Burning (like the pulse in the artery)

- ***Summary*:**
  <u>Aspirin</u>
- **Uses :**
  1. Anti-inflammatory
  2. Analgesics
  3. Antipyretic
  4. Anti-coagulant (prevents platelets aggregation)

- **Side effects**: peptic ulcer
- **Mechanism:** COX inhibitor

Sorry for any mistake

Wish you hyper LUCKemia~