بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | FINAL 4

NSAIDs

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NSAID Analgesics

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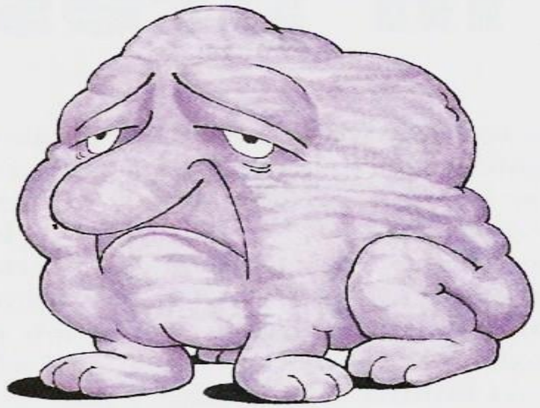
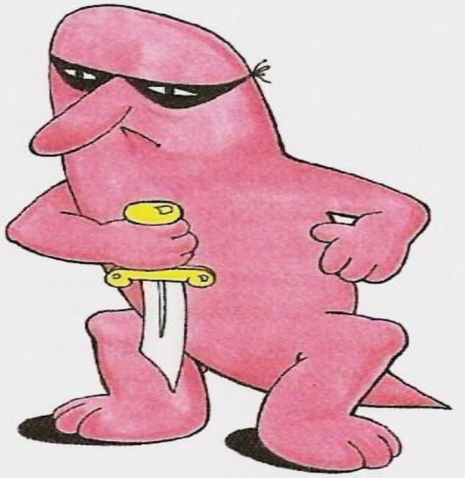
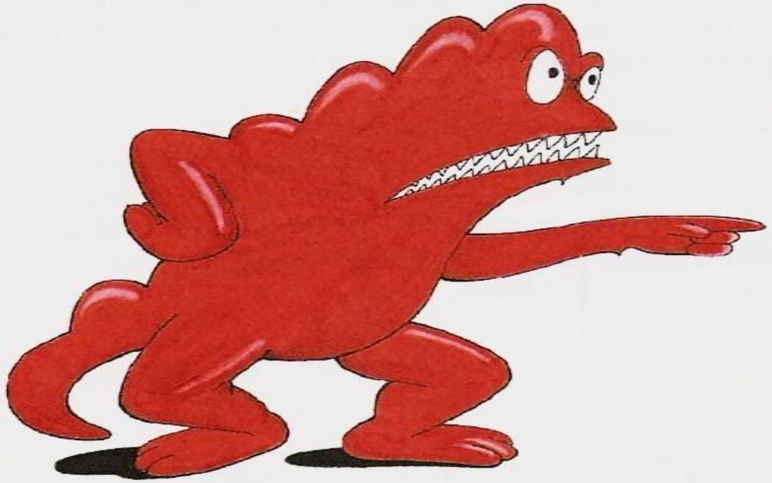
sharp pain



dull aching pain

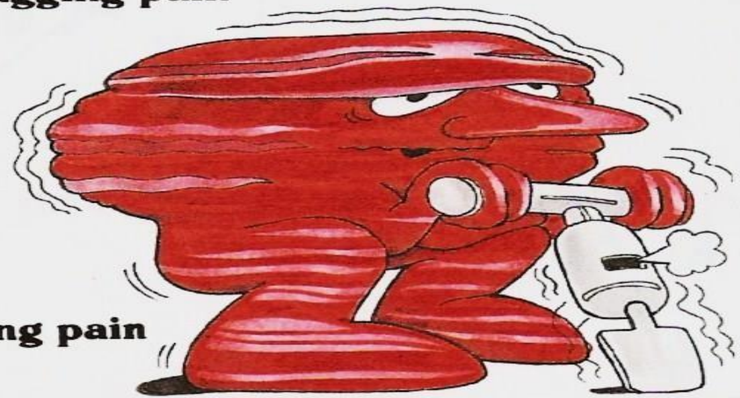


stabbing pain



nagging pain

burning pain



throbbing pain

boring pain

Pain

- Universal, Complex, Subjective experience

- No. 1 Reason people take medications

- Generally is related to some type of tissue damage and serves as a warning signal.

- Pain is the **main reason** people seek treatment for.
- Imagine there is no pain, the infections will accumulate in your body because you don't know about them and may kill you at the end. So, pain makes us feel about the infection and seek treatment.

Analgesics

Drugs That **Suppresses pain** to reach **Analgesia –>** (no more pain state).

- **Pain killers.**

- Derived from Greek **an-** "without" & **-algia** "pain".

- An **analgesic**, or **painkiller**, is any member of the group of drugs used to achieve analgesia — relief from pain.

- Drugs that relieve pain **selectively *without*** blocking the conduction of nerve impulses, markedly altering sensory perception, or affecting consciousness.

- Act in various ways on the **peripheral and central nervous systems.**

Analgesics

- **Definition of Pain :**

Unpleasant sensation that can either be **chronic or acute**. Usually, pain happens because of changes that are happening in our body such as **neurochemical processes.**

Think about it as an alarm that can start out in your **limbs & organs (Peripheral N.S)** or in the **brain** & **spinal cord (Central N.S)**, Drugs that reduce pain are called **Analgesics**.

- **The Difference between Analgesic & Anesthesia :**

Analgesics relive pain **selectively without** causing a loss of consciousness or affecting (altering) your sensory perception like touching or blocking nerve impulses

While **Anesthesia does the opposite, it involves total loss of sensation & consciousness.**

Let's Break Down The Concept :

- ***Selectively*** = These Drugs specifically target the chemical pathway that signals the pain.
- ***Without Blocking Conduction of Nerve Impulses*** = Your Nerves still function normally.
- ***Don't Change (Alter) sensory perception or Consciousness*** = you stay fully awaked and aware.

Analgesics

- **Analgesics has 2 main Categories :**

1- **NSAIDs :** Works on **Peripheral N.S** – we use them a lot on mild/moderate pain
- They affect **Prostaglandins Synthesis.**

2- **Opioids :** Works on specific Receptors in **Central N.S** called **Opioids Receptors**
- They modulate sensation by modulating these Receptors. **Used in severe pain.**

- The non-steroidal anti-inflammatory drugs (NSAIDs)

- Paracetamol = acetaminophen → **Paracetamol is in a separated group, although it inhibits PG synthesis as NSAIDs,** but it has some special characteristics that will be explained.

- Opioid drugs

Comparison of Analgesics

Understand this table :

Feature	Narcotic (Opioids)	Nonnarcotic (nonopioid) Belongs to NSAIDs
Efficacy	Strong	Weak
Prototype	Morphine	Aspirin
Pain Relieved	Any Type	Musculoskeletal
Site of Action	Central (Only CNS)	Peripheral and Central
Mechanism	Specific Receptors	PG Synthesis
Danger (Side Effects)	Tolerance & Dependence	G.I irritation
Anti-inflammatory	No	Yes
Antipyretic	No	Yes
Antiplatelets	No	Yes

Comparison of Analgesics

Comparison	Nacrotic (opioids)	Non-Narcotic (non-opioids)
Target	work only on CNS	Mainly Peripheral N.S but some could work on CNS
Mechanism	bind to opioid receptors in CNS to block it	Inhibiting the synthesis of prostaglandins.
Efficacy	Strong, they can relieve any type of pain but with a higher risk of dependency	Weaker (Lower).
Usages	ONLY Analgesics	Analgesics Anti-Inflammatory Antipyretics Antiplatelets

We will focus on Non-Narcotic

NSAIDs

- The NSAIDs are a group of **chemically dissimilar agents** that differ in their **antipyretic**, **analgesic**, and **anti-inflammatory** activities.

- **Inhibiting** the **cyclooxygenase** enzymes that catalyze the first step in prostanoid biosynthesis.

  >>>> **Decreased** prostaglandin synthesis with both **beneficial** and **unwanted** effects.

Explained in Next slide

NSAIDs

- They are chemical compounds that share :

  - **Different** Chemical Structures.

  - **Similar** Properties (Activities) which are :

    1) Analgesic = Painkillers.
    2) Antipyretic = Reduce elevated body Temperature.
    3) Anti-Inflammatory Activities.

  - **Mechanism of action :**

    - They **block** an enzyme called **cyclooxygenase (COX).**

    - In normal biochemistry , COX enzyme is a part of **arachidonic acid** metabolism and responsible for producing **prostaglandins** (prostanoids) **which has a role in pain, fever & inflammation,** so NSAIDs **block** this pathway to **reduce these unpleasant symptoms.**

Inflammatory pathways

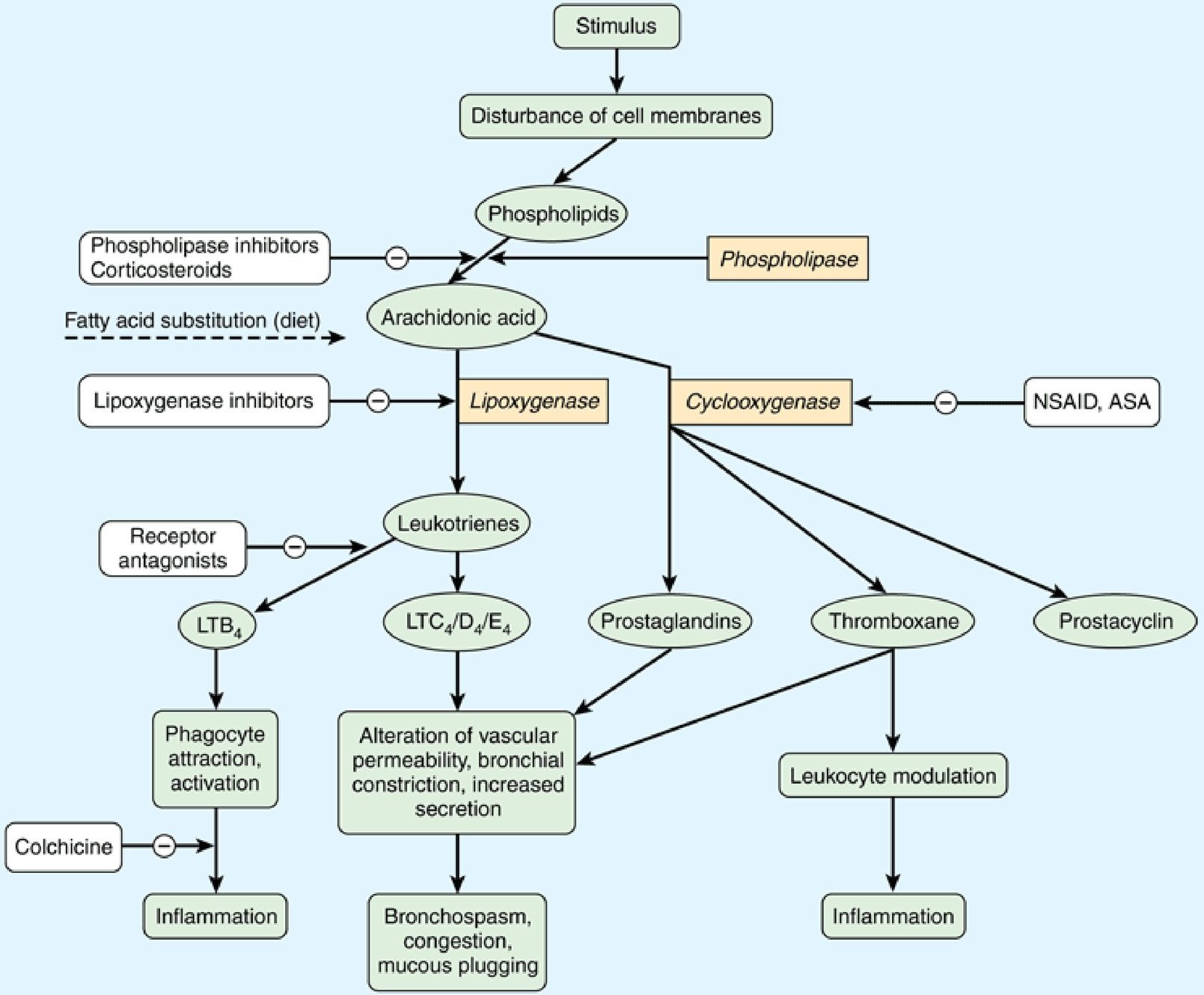
- **Cyclooxygenase** (COX) pathway of **arachidonate** metabolism produces **prostaglandins**.

- Effects on blood vessels, on nerve endings, and on cells involved in inflammation.

- The **lipoxygenase** pathway of **arachidonate** metabolism yields **leukotrienes**.

- Have a powerful chemotactic effect on eosinophils, neutrophils, and macrophages and promote **bronchoconstriction** and **alterations in vascular permeability.**

Explained in THE UPCOMING slides



Explained in next slide

Inflammatory pathways

- it starts with a stimulus like injury or infection that causes disturbance in cell membranes. This event activates an enzyme called **Phospholipase** which will act on the phospholipids in cell membrane converting it to **Arachidonic acid**.
- **Once Arachidonic acid is released, the pathway *splits into 2 main branches* each has a different enzyme :**

- **Cyclooxygenase pathway (by COX enzyme) :**

    - COX takes arachidonic acid and convert it into three main products :
    - **1) Prostaglandins 2) Thromboxane 3) Prostacyclin,** all of them are ***prostanoids***
    - These products cause alteration in **vascular permeability** (causing swilling, edema), **leukocyte modulation, and inflammation**

- **Lipoxygenase pathway (by LOX enzyme) :**

    - LOX converts Arachidonic Acid into **leukotrienes** which will branch into 2 specific types :
        - **LTB4** => Attracts & activates phagocytes (immune cells) leading to inflammation
        - **LTC4-LTD4-LTE4 :**

          1) cause bronchial constriction.
          2) alteration of vascular permeability (EDEMA).
          3) Increased secretion – in airways glands which will produce more mucus.
          NOTE : Prostaglandins share some of these effects.

Inflammatory pathways

Drugs that inhibits this pathway :

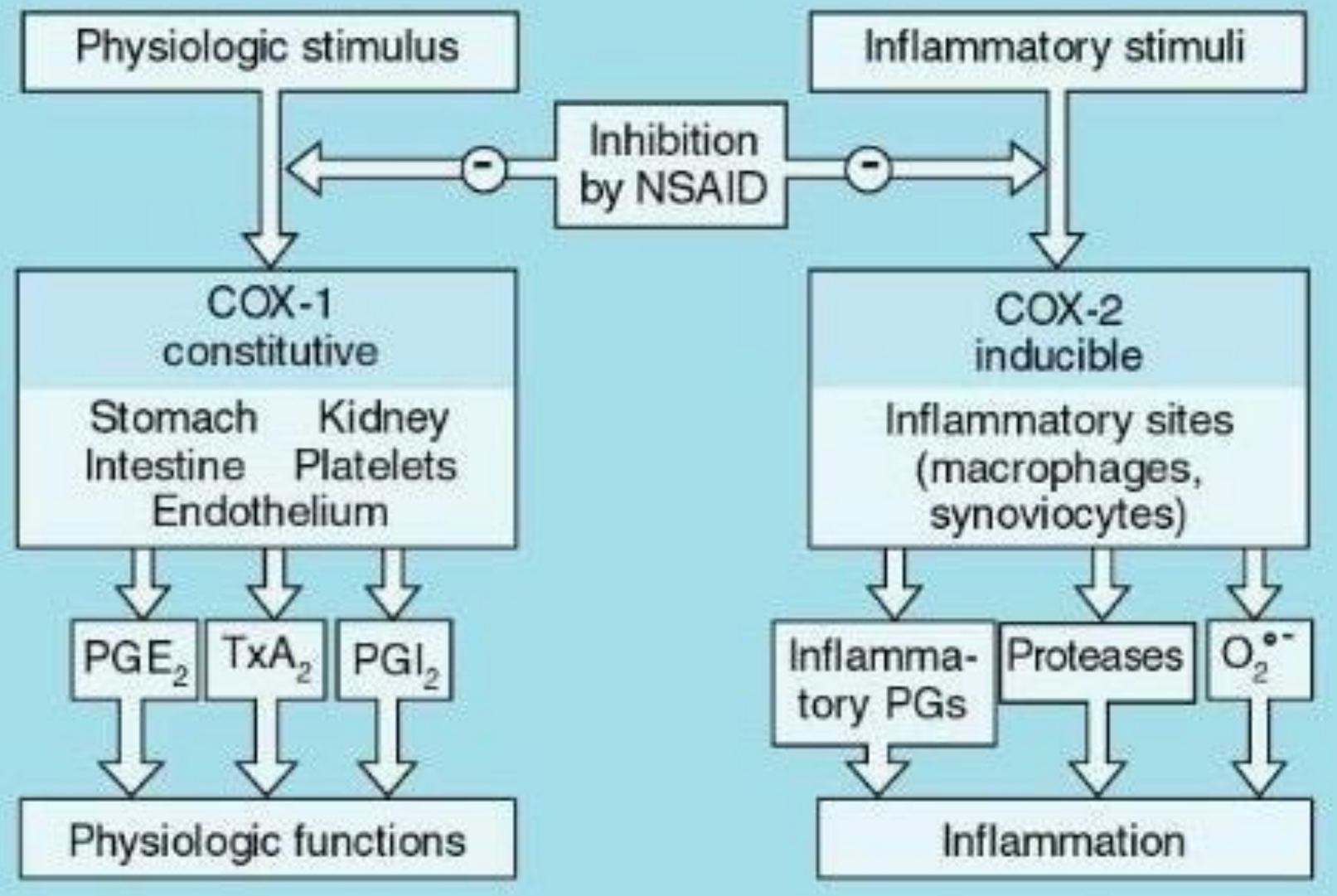
1) ***Corticosteroids :***

- **Target Enzyme** : phospholipase
- **Mechanism** : Inhibits the converting of phospholipids to Arachidonic Acid
- **Outcome** : Shutting down the entire inflammation cascade before it even starts.

2) ***NSAIDs & Aspirin (ASA) :***

- **Target Enzyme** : cyclooxygenase (COX)
- **Mechanism** : Inhibits converting of Arachidonic Acid to PG, Thromboxane & Prostacyclin
- **Outcome** : Reduce Pain and inflammation.

3) ***Lipoxygenase Inhibitors*** (Block the enzyme itself).



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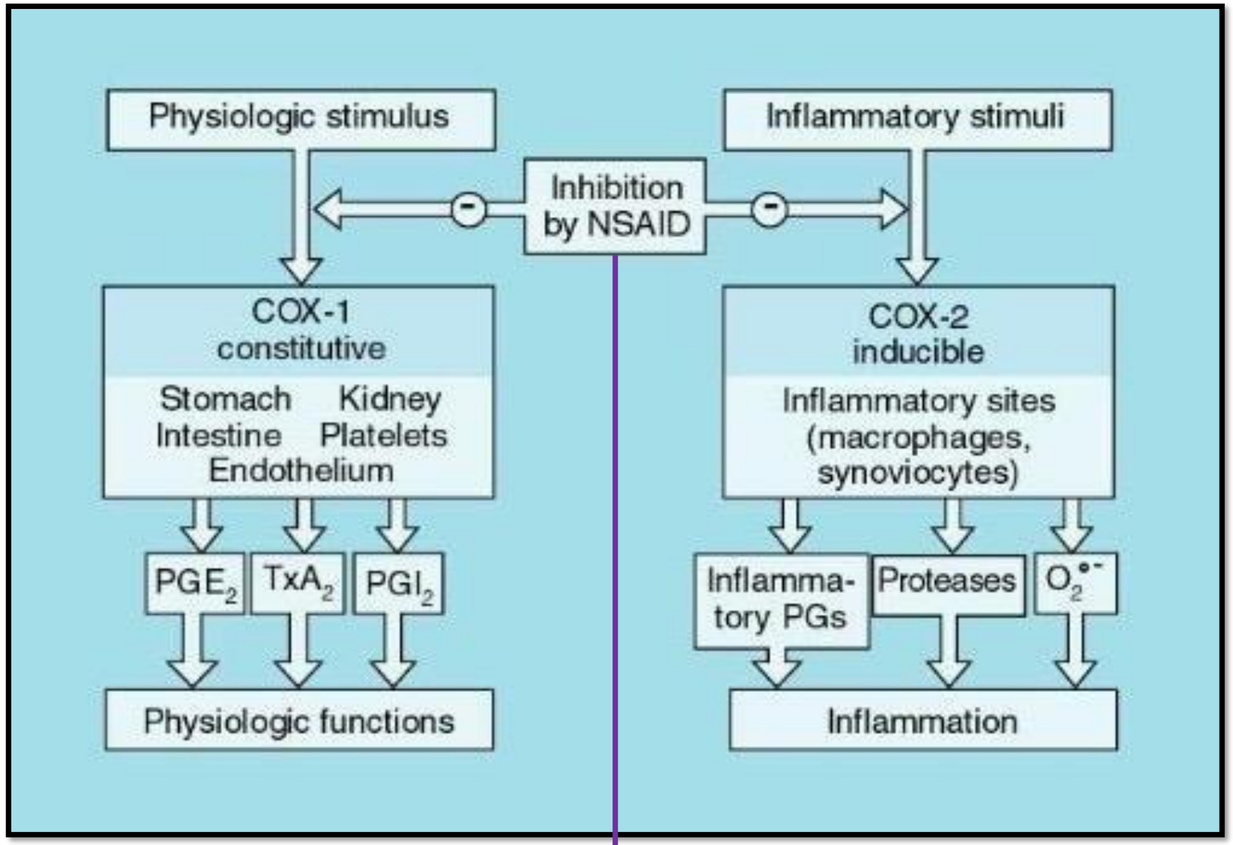

NSAIDs Dilemma :

As you know now, we have COX1 and COX2 in our bodies. NSAIDs will block both because these are 'non-selective' drugs, leading to 2 main effects :

- **Therapeutic effect** = By blocking **COX2** you will stop the inflammatory PGs resulting in reduced pain and swelling.

- **Unwanted side effect** = NSAIDs also block **COX1** (the 'good' type) this will stop its normal work leading to unpleasant side effects such as GI irritation.

Inflammatory pathways

Isoforms of COX : It has 2 main isoforms COX1 & COX2 :

1) **COX1** = Normal Physiological Requirement. It is **CONSTITUTIVE** which means it is always present in tissues under **normal conditions**. Founded in vital areas such as stomach, intestine, endothelium, kidneys & platelets. It produces specific **Prostanoids** : **PGE2** + **TXA2** (Thromaboxane) + **PGI2** (Prostacyclin).

   - PGE2 **protects the stomach from excessive acid secretion by increasing mucus secretion and lowering the acid**, so when **we inhibit COX1,** PGE2 will **stop its function** and **acid will increase inside, this tells us why NSAIDs have G.I irritation as a side effect**

2) **COX2** = It is inducible, usually it is not found in normal condition. Once an inflammatory stimuli such as an infection or an injury. off, and you **can't find it without inflammation**, once there is a trigger it will turn on and become activated (induced). It is heavily found at inflammatory sites specifically in immune cells such as **macrophages** and joint cells like **synoviocytes**.

   - It produces inflammatory **PGs,** tissue-damaging **Proteases** and **ROS (superoxide radicals).**

Cyclo-oxygenase (COX)

- Exists in the tissue as **constitutive isoform (COX-1).**
- At site of inflammation, cytokines stimulates the induction of the **2nd isoform (COX-2).**
- **Inhibition of COX-2** is thought to be due to the **anti-inflammatory actions of NSAIDs.**
- **Inhibition of COX-1** is responsible for their **GIT toxicity**.
- Most currently used NSAIDs are **somewhat selective for COX-1,** but selective **COX-2 inhibitors are available.**

- We are trying to develop drugs that works only on **COX2** (Selective COX2) only. This is good, COX1 side effects issue will be solved but for now most NSAIDs works on COX-1 which causes GI irritation and more side effects.

Non-steroidal anti-inflammatory drugs (NSAIDs).

As discussed, all **NSAIDs share common activities in inhibiting** :

1) Pain.
2) Fever.
3) Inflammation.

By inhibition of cyclo-oxygenase enzymes COX-1 & COX-2.

- **COX:**

- **COX-1** is involved in tissue hemeostasis, platelet aggregation, gasric cytoprotection.
  - **Normally** Founded (Physiologically) in all tissues

- **COX- 2** is responsible for the production of mediators of inflammation.
  - Founded heavily at **inflammation sites**
  - **Must be induced**

NSAIDs

An anti-inflammatory action :

(1) **decrease Vasodilator PG (PGE_2, PGI_2)** leads to less vasodilatation and, indirectly, less edema.

(2) The inhibition of activity of adhesion molecule.

(3) Accumulation of inflammatory cells is also reduced.

1) Normally, **PGE2 & PGI2 causes vasodilation and increase permeability**, by decreasing these PGs, NSAIDs keep the blood vessels normal-sized so **less blood will flow** and less leakiness meaning less fluid buildup >> **preventing edema.**

2) During an injury, blood vessel walls express **adhesion molecules** that catch a white blood cell passing nearby so they can enter the injured tissue. NSAIDs **inhibit this sticky feature**, meaning WBCs cannot stick and go to the injured site because **normally, immune cells can't stick to the vessel walls without this help**. By that, NSAIDs will reduce the accumulation of inflammatory cells at the site.

NSAIDs

An analgesic effect:

- **Decreased prostaglandin** generation means **decrese sensitivty** of **nociceptive** nerve endings to inflammatory mediators.
  Nociceptive Nerves = **Pain** Nerves
- Relief of **headache** is due to **decreased prostaglandin-mediated vasodilatation.**

- **Relief Pain :**
  - PG normally make pain nerves (Nociceptors) **extra sensitive,** without PG these nerves are **less** easily triggered, so now they are less sensitive meaning you will feel **less pain. NSAIDs reduce PG generation by that the pain will also decrease.**

- **Relief Headache :**
  - Normally, PGs **cause blood vessels In the head to widen – vasodilation. This widening creates headache.**
  - NSAIDs **block PGs,** so now blood vessels will go back to normal size **relieving the pressure and pain.**

NSAIDs

An antipyretic effect:

This is partly due to a **decrease in the mediator prostaglandin** that is **responsible for elevating the hypothalamic set-point** for temperature control in fever.

- The Hypothalamus in the brain **handles the internal thermostatic state** keeping our body at a normal Temperature (consider it as 37C).

- When you get sick, the body produces **specific prostaglandins (PGE2)**. They will go to the hypothalamus and **raise the target (Normal Temp) to become higher e.g 38.5C.** Because of that you will start **feeling cold, your temp is 37.9 but now the normal is 38.5C,** so you start shivering to generate heat which is the fever to increase the temperature.

- Now, NSAIDs fix this by blocking the production of **these specific PGs**, this remove the trigger and will reset your hypothalamus **making the Temperature normal again at 37C and the fever is solved.**

Classification

- Non-selective COX inhibitor

  These include most NSAIDs. (though some have sligh preference or selectivity for either COX-1 or COX-2).

- Selective COX inhibitor

  Celecoxib

  Rofecoxib (no longer used)

  Meloxicam

Aspirin

The prototype of NSAIDs

- It can cause **irreversible** inactivation of COX-1 and COX-2.

  Most NSAIDs block COX enzyme temporarily. Aspirin on the other hand, blocks it **permanently** so the body **must produce new enzymes to regain the function.** That is why it's effect will **last longer** comparing other drugs.

- Aspirin is the **prototype** of **traditional** NSAIDs and was officially approved by the FDA in 1939.

  Aspirin comes from modified natural sources especially from acetylsalicylic acid which is an important material in the bark of the willow tree. It is known since the ancient civilizations as they used to use the bark of the willow to relief pain and inflammation without knowing it's mechanism

- It is one of the **most** commonly NSAIDs used and is the drug to which all other anti-inflammatory agents are compared

  It is the prototype of NSAIDs, meaning it is very strong & every new drug will be compared with it to see if it is stronger or weaker than aspirin

Mechanism of action

- Aspirin is a weak organic acid that is unique among the NSAIDs in that it **irreversibly inactivates cyclooxygenase.**

- **The other NSAIDs are all reversible.**

- Aspirin is **rapidly deacetylated by esterases** in the body producing **salicylate**, which **has anti-inflammatory, antipyretic, and analgesic effects.**

➢ When aspirin enters your blood stream, it will be deacetylated extremely fast by esterases leaving the salicylate which will provide 3 effects to the body :

1) ***Antipyretic.***
2) ***Anti-Inflammation,***
3) ***Analgesic.***

Mechanism of action

- Main Feature :

  - Aspirin irreversibly (permanently) blocks and inactivates COX but all other NSAIDs block them temporarily.

  - Also, the effect of the aspirin is much longer than the other NSAIDs, that because the body must produce new enzymes. **Even if the body washed the aspirin out, it's effect will still available until the body produce new enzyme.**

Asprin

- The antipyretic and anti-inflammatory effects of salicylate are due primarily to the blockade of **prostaglandin** synthesis at the **thermoregulatory** centers in the **hypothalamus** and **at peripheral target sites.**

- Furthermore, by decreasing **prostaglandin** synthesis, salicylate also prevents the sensitization of pain receptors to both mechanical and chemical stimuli.

- Aspirin may also depress pain stimuli at **subcortical** sites

Analgesic action:

- Prostaglandin E2 (PGE2) is thought to **sensitize** nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process.

- management of pain of **low to moderate intensity arising from musculoskeletal disorders** rather than that arising **from the viscera.**

- **PGE2, Histamine & Bradykinin** are produced by your body when any tissue gets damaged.

- The moment your tissue is damaged, your body releases Histamine & Bradykinin. They cause **immediate** swelling, redness, and pain.

- PGE2 is produced by the inflammatory pathway after the first step. It **amplifies** the pain by making nerves extremely sensitive.

- NSAIDs such as ibuprofen or aspirin are used in treating **mild to moderate pain**.

- They are **not strong** for treating severe pain & they are **not highly effective** for **internal organs (viscera)** pain such as kidneys stone pain (we use opioids for severe or visceral pain).

- NSAIDs **work perfectly** on Musculoskeletal disorders such as muscles, joints, tendons & arthritis pain.

Antipyretic action:

- Fever occurs when the set-point of the **anterior hypothalamic thermoregulatory center is elevated.**
- **Impeding PGE2** synthesis and **releaseresets the hypothalamus toward normal.**
- At higher doses it rapidly lowers the body temperature of febrile patients by increasing heat dissipation as a result of peripheral vasodilation and sweating. (VSMC).
- Aspirin has **no effect on normal body temperature.**

Antipyretic action:

➢ How fever happens ?

- **Anterior Hypothalamic** has a standard normal temperature called the **set-point** which is normally 37C in normal conditions.

- Once you become sick, PGE2 is produced and then travels to the brain as a chemical messenger. By that, your set-point will **increase** to a higher temperature. And your body will try to reach the new set-point.

✓ **Blocking PGE2** will stop this event. Resulting in **resetting** back your hypothalamus **thermoregulatory** center back to normal.

- Now, the body must **get rid of the extra temperature**, and that happens by 2 main ways :

  - ***Sweating*** : evaporation cools your body down.
  - ***Peripheral Vasodilation*** : the blood vessels near the skin will become wider (Relaxed Vascular smooth muscles cells, VSMC) this will cool down your body.

Antipyretic action:

- **Important Safety Feature of Aspirin :**
  - We said that it cools your body when the set-point is raised. What if we take it without any fever or raised set-point, in normal conditions ? **NOTHING WILL HAPPENS**. Aspirin will **not affect** your normal daily temperature at the normal set-point !

- Why ?
  - NO Trigger to start inflammatory pathway = No PGE2 produced = Set-point is normal = aspirin has no PGE2 to work on = no effect.

Respiratory actions:

- At therapeutic doses, aspirin **increases alveolar ventilation**. uncouple oxidative phosphorylation, which leads to **elevated CO2** and increased respiration.

- **Higher doses** work directly on the **respiratory center** in the medulla, resulting in **hyperventilation and respiratory alkalosis.**

- At **toxic** levels, **central respiratory paralysis >> acidosis.**

Respiratory actions:

1) *Effects of **Therapeutic Doses*** :

- Aspirin causes uncoupling of Oxidative phosphorylation, making the mitochondria work inefficiently so less ATP is produced. **The body will start burning O2 faster producing excess heat and CO2. To get rid of CO2, you will start breathing faster and deeper (increased alveolar ventilation)**

2) *Effects of **Higher Doses (Moderate Toxicity)** :*

- Higher Doses makes Aspirin crosses into the brain and directly stimulates the respiratory center located in the medulla in the brainstem. This direct stimulation **causes hyperventilate (Breathing rapidly and deeply).**

- Breathing Fast decreases CO2 which is an acid. So, losing CO2 means less acidic =more basic blood and this is called **respiratory alkalosis** condition.

3) *Effects of **Toxic levels (Severe, Life-threatening toxicity);***

- Causes Severe depression as the respiratory center shuts down (**Central respiratory paralysis**).

- Breathing will **slow** down and it could stop. By that, **CO2 builds up rapidly in the blood**, creating a highly acidic environment which is a medical emergency called (**Acidosis**).

Toxicity of salicylates

- (1) stimulation of the respiratory center of the brain, leading to hyperpnea and respiratory alkalosis

  Hyperpnea (Fast Breathing) = less CO2 = Higher pH = Respiratory Alkalosis.

- (2) uncoupling of oxidative phosphorylation, leading to increased oxygen utilization and glucose demand, increased gluconeogensis, and increased heat production

  Disrupt the ability to produce ATP, body use more oxygen and burn glucose rapidly, the energy is released as heat (Hyperthermia)

- (3) inhibition of Krebs cycle enzymes, leading to decreased glucose availability and increased organic acids

  Krebs Cycle is inhibited, less ATP is produced so the body switches to anaerobic metabolism producing lactic acid and break down of lipids to ketones, all of this results in metabolic acidosis

- (4) alterations in lipid metabolism and amino acid metabolism, enhancing metabolic acidosis.
- (5) increased fluid and electrolyte losses, leading to dehydration, sodium depletion, potassium depletion, and loss of buffer capacity.

- Caused By:
  1) Hyperventilation -> dehydration
  2) Sweating -> Fluid/electrolyte loss
  3) Kidneys -> NA+ / K+ / bicarbonate out with urine.

Gastrointestinal effects:

Mucus Protects the stomach from its Acid.

- **PGE2** stimulate synthesis of protective **mucus** in both the **stomach and small intestine.**
- In the presence of aspirin, these prostanoids are not formed, resulting in **increased gastric acid secretion and diminished mucus protection.**
- Agents used for the prevention of gastric and/or duodenal ulcers include **proton-pump inhibitors (PPIs)**; esomeprazole, lansoprazole, omeprazol
- At stomach pH, aspirin is uncharged; consequently, it readily crosses **into mucosal cells, where it ionizes (becomes negatively charged) and becomes trapped, thus potentially causing direct damage to the cells.**

- **Aspirin is a weak acid**, and the stomach has a **low pH (very acidic)**, so aspirin stays uncharged there.
- It is **fat soluble** so it will easily enter the cell membrane of mucosal cells lining in the stomach.
- **Inside the cell** is normal physiological PH, so **aspirin will become charged now.**
- Know that charged molecules can't enter or leave cell membrane **so aspirin will accumulate inside the mucus cell leading to cell death.**

Effect on platelets:

- **TXA2** enhances platelet aggregation >> **Low doses 81 mg** daily of aspirin can **irreversibly inhibit** thromboxane production in platelets via **acetylation of cyclooxygenase.**

- Because platelets **lack nuclei, they cannot synthesize new enzyme**, and the **lack of thromboxane persists for the lifetime of the platelet (7 days) >>** As a result **prolonged bleeding time.**

- In the inflammation pathway, COX1 produces TXA2 which enhances platelet aggregation in bleeding conditions.

- Aspirin as we said, has a prolonged effects because of the permanent blockage of the enzyme. So, the body must produce new ones. However, **platelets lack nuclei that produces new enzymes,** so to regain the enzyme, we need to **wait until this platelet lifetime expires and a new one will give us the enzyme.**

Actions on the kidney:

استغفر الله العظيم وأتوب إليه

- Cyclooxygenase inhibitors prevent the synthesis of PGE2 and PGI2 that are responsible for maintaining **renal blood flow.**
- Decreased synthesis of prostaglandins can result in **retention of sodium and water** and may cause **edema** and **hyperkalemia** in some patients.
- **Interstitial nephritis** can also occur with all NSAIDs but less with aspirin (specially at low dose).

Therapeutic uses

- The salicylic acid derivatives (such as aspirin) are used in the treatment of gout, rheumatic fever, osteoarthritis, and RA .

- Commonly treated conditions requiring **analgesia** include headache, arthralgia, and myalgia (any kind of pain associated with MSS) .

External applications :

- Salicylic acid is used topically to treat corns and warts because it has a keratolytic ability.

Cardiovascular applications:

- Aspirin is used to inhibit platelet aggregation. Low doses are used **prophylactically** to.

- reduce the risk of recurring transient ischemic attacks (**TIAs**) and stroke or death. A lot of patients who have a history of cardiovascular diseases, such as hypertension, as well as elderly patients or those with diabetes, are often prescribed aspirin. This is because aspirin has a prophylactic effect in protecting the cardiovascular system by reducing the risk of ischemic attacks and thrombotic events.

- Studies have shown a **reduced risk of death** in those having an acute **myocardial infarction**

PHARMACOKINETICS

Administration and distribution:

- After oral administration, the un-ionized salicylates are passively absorbed from the **stomach** and the **small intestine.** They can also be administered as suppositories, allowing rectal absorption.

- **Rectal** absorption of the salicylates is **slow** and unreliable, but it is a useful route for administration to vomiting children.

- Salicylates must be avoided in children and teenagers (<15 years old (sometimes <12 years)) with varicella (chickenpox) or influenza to prevent **Reye's** syndrome, which can be a fatal disorder. The exact cause of this syndrome is not known. Instead, paracetamol can be used, as it is considered one of the safest drugs for use in these patients.

- Salicylates are highly protein bound.

Dosage:

- The salicylates **exhibit analgesic activity at low doses; only at higher doses do these drugs show anti-inflammatory activity.**

- For example, two 325-mg aspirin tablets administered four times daily produce **analgesia**, whereas 12 to 20 tablets per day produce both analgesic and **anti-inflammatory** activity.

- For long-term **myocardial infarction prophylaxis**, the dose is 81 to 162 mg/day (approximately one to two tablets of low-dose aspirin).

- For those with **RA or osteoarthritis**, the initial dose is 3 grams/day.

- for **stroke prophylaxis**, the dose is 50 to 325 mg/day.

Note: The doctor mentioned that we are not required to memorize the exact doses of each drug. However, it is important to remember that aspirin is used at lower doses for antiplatelet activity (usually around 81 mg/day and generally less than 325 mg/day). In contrast, higher doses (≥325 mg and sometimes up to about 3 g/day) are used when the goal is analgesic or anti-inflammatory effects.

Metabolism and excretion

- At dosages of 650 mg/day, aspirin is hydrolyzed to salicylate and acetic acid by esterases in tissues and blood.

- Salicylate is converted by the **liver** to water-soluble conjugates that are rapidly cleared by the **kidney**

- Both **hepatic** and **renal** function should be monitored periodically in the receiving long-term, high-dose aspirin therapy.
- aspirin should be avoided in patients with a creatinine clearance of less than 10 mL/min.

Other side effects

Hypersensitivity: Approximately 15 percent of patients taking *aspirin experience hypersensitivity reactions*.

- Symptoms of true allergy include **urticaria**, **bronchoconstriction**, or **angioedema. Fatal anaphylactic shock is rare.**

Reye's syndrome:

- Aspirin and other salicylates given during viral infections has been associated with an **increased incidence of Reye's syndrome, which is an often fatal, fulminating hepatitis with cerebral edema.**

- This is especially encountered in children, who therefore should be given acetaminophen instead of aspirin

Drug interactions:

- Salicylate is 90 to 95 percent protein bound, mainly to plasma protein such as albumin,and can be displaced from its protein-binding sites, resulting in increased concentration of free salicylate. Any drug that also binds to albumin or plasma proteins can interact with aspirin, such as warfarin.

- alternatively, aspirin could displace other highly protein-bound drugs, such as **warfarin**, **phenytoin**, or **valproic** acid, resulting in higher free concentrations of the other agent .Therefore, we must be careful when co-administering aspirin with these important drugs, as warfarin is an anticoagulant and phenytoin and valproic acid are used to treat epilepsy.

- Concomitant use of **ketorolac** and aspirin is contraindicated because of increased risk of GI bleeding and platelet aggregation inhibition.

Aspirin and pregnancy

- In pregnancy: Aspirin is classified as FDA pregnancy category C risk during Trimesters 1st and 2nd .

- category D during 3rd Trimester

  ✓ Usually, aspirin is avoided during pregnancy, but in some women with a history of miscarriages due to immune-mediated rejection of the fetus, a low dose of aspirin may be encouraged during the first trimester to improve fetal circulation.

- Because salicylates are excreted in breast milk, aspirin should be avoided during pregnancy and while breast- feeding.

Reye's syndrome

- Reye's syndrome is a potentially fatal disease that has numerous detrimental effects to many organs, especially the brain and liver, as well as causing a lower than usual level of blood sugar (hypoglycemia) The classic features are a rash, vomiting, and liver damage. The exact cause is unknown and, while it has been associated with aspirin consumption by children with viral illness, it also occurs in the absence of aspirin use.

Propionic acid derivatives (other non-steroidal anti-inflammatory drugs)

- **Ibuprofen, naproxen, fenoprofe, ketoprofen, flurbiprofen.**
- All these drugs possess anti-inflammatory, analgesic, and antipyretic activity.
- their **GI** effects are generally less intense than those of aspirin.
- These drugs are **reversible** inhibitors of the cyclooxygenases.
- All are well **absorbed** on oral administration and are almost totally bound to serum **albumin.**
- They undergo **hepatic** metabolism and are excreted by the **kidney**.
- The most common adverse effects are **GI** irritation, ranging from dyspepsia to bleeding.

Propionic acid derivatives (other non-steroidal anti-inflammatory drugs)

- Side effects involving the central nervous system (**CNS**), such as headache, tinnitus, and dizziness, have also been reported.

- The use of sulindac has also been linked to cases of acute pancreatitis.The use of dimethylsulfoxide (DMSO) topically in combination with sulindac has been reported to induce severe neuropathies.

Naproxen and Ibuprofen

- Pregnancy : category C, category D **(in the third trimester).**
- Increase the risk of cardiovascular thrombotic event, MI and stroke.

- Increase risk of GI bleeding.

- Ibuprofen not exceed 3200mg/day., and take with food or with water to avoid GI effect.

- Asthmatic patient. **Their use in asthmatic patients is contraindicated or should be given with caution. This is related to the arachidonic acid pathway. When cyclooxygenase (COX) is inhibited by NSAIDs, more arachidonic acid becomes available for the lipoxygenase (LOX) pathway. This results in increased production of leukotrienes. Leukotrienes can exacerbate asthma because they cause bronchospasm, bronchial edema, and increased mucus secretion, which worsen the asthmatic response.**

Acetic acid derivatives

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- **Indomethacin , sulindac , Etodola.**
- All have anti-inflammatory, analgesic, and antipyretic activity.
- They act by reversibly inhibiting cyclooxygenase.
- Despite its potency as an anti-inflammatory agent, the toxicity of indomethacin limits its use to the treatment of acute gouty arthritis, ankylosing spondylitis.
- The adverse reactions caused by sulindac are similar to, but less severe than, those of the other NSAIDs, including indomethacin.
- Etodolac has effects similar to those of the other NSAIDs.

Indomethecin

- acute and chronic rheumatoid arthritis and osteoarthritis.
- Also useful in ankylosing spondylitis, acute gouty arthritis, bursitis, and tendinitis.
- Side effects:
  - It produces more CNS side effects than most of the other NSAIDs. Severe headache occurs in 25 to 50% of patients; vertigo, confusion, and psychological disturbances
  - GI symptoms also are more frequent.
  - Hematopoietic side effects (e.g., leukopenia, hemolytic anemia, aplastic anemia, purpura, thrombocytopenia, and agranulocytosis
  - Ocular effects (blurred vision, corneal deposits) Hepatitis, jaundice, pancreatitis, and hypersensitivity reactions

Oxicam derivatives

- ***Piroxicam*** *and* ***meloxicam***
- *are used to treat RA, ankylosing spondylitis, and* osteoarthritis .
- They have **long half-lives**, which permit once-daily administration, and the parent drug as well as its metabolites are renally excreted in the urine.
- ***Meloxicam inhibits both COX-1 and COX-2****, with* ***preferential binding for COX-2***, and at **low to moderate** doses shows **less GI irritation than** ***piroxicam and*** **other non-steroidal anti-inflammatory drugs** .

Fenamates

- ***Mefenamic***.
- *Have* ***no advantages*** *over other* NSAIDs as anti- inflammatory agents.(they share the same mechanism of action and the same effects as other NSAIDs).
- Their side effects, such as **diarrhea**, can be severe, and they are associated with inflammation of the bowel.
- Cases of hemolytic anemia have been reported.

Heteroaryl acetic acids

- From this group of drugs, the most commonly used are diclofenac sodium and diclofenac potassium.

- ***Diclofenac and tolmetin , ketorlac***

- *are approved for long-term use in the treatment of RA,* osteoarthritis .

- ***Diclofenac*** *is more potent than indomethacin or naproxen.*

- *An* ***ophthalmic*** preparation is also available .

- *Diclofenac accumulates in synovial fluid, and the primary route of excretion for the* drug and its metabolites is the **kidney** . Because diclofenac accumulates in the synovial fluid, it is highly recommended for use in inflammatory conditions of the joints.

Diclofenac sodium

- Used PO 50mg after food, I.M. inj 75mg (different formulation)
- Diclofenac potassium is prompt release and has quicker onset where as the Diclofenac sodium is delayed release.
- Pregnancy: category C

Diclofenac sodium

- C/I
- **Side effect :** Hypersensitivity.
- Asthmatic patient and Patient with history of peptic ulcer **are contraindicated for the use of diclofenac sodium.**
- Metabolism: liver.
- Excretion: urine.

Selective COX-2 inhibitor

❑ Celecoxib

Historically, selective COX-2 inhibitors are relatively newer drugs. They were developed in the late 20th century and approved in the early 21st century (around the year 2000). **Two drugs were introduced from this class: celecoxib** and rofecoxib.

- more selective for COX-2 than for COX-1 .
  These drugs were developed to avoid the gastrointestinal (GI) side effects associated with the non-selective inhibition of cyclooxygenase.

- Adverse effects are slighter than other NSADs.

- Long-term studies of the incidence of clinically significant gastrointestinal ulcers and bleeding are not yet completed.
- May increase the incidence of edema and hypertension.

Selective COX-2 inhibitor

- However, after their release on the market, rofecoxib was withdrawn because it was associated with an increased risk of death related to thromboembolic events. Celecoxib, however, is still available in different commercial forms (such as Celebrex). It is indicated for chronic inflammatory conditions such as rheumatoid arthritis.

- Although celecoxib reduces inflammation and pain with fewer gastrointestinal side effects than non-selective NSAIDs, it may still be associated with thromboembolic events. This is related to the imbalance between thromboxane and prostacyclin production, which may promote platelet aggregation and increase the risk of thrombosis.

- For this reason, celecoxib carries a **black box warning**. This warning indicates that special caution should be taken when using this drug in patients who are prone to thromboembolic events. A black box warning represents a very serious safety warning that appears on the drug label to alert both physicians and patients about significant risks, and such drugs should only be used when prescribed by a physician.

Acetaminophen distinct group of analgesics

- Acetaminophen inhibits prostaglandin synthesis in the **CNS.**
- This explains its antipyretic and analgesic properties.
- Acetaminophen has less effect on cyclooxygenase in peripheral tissues, which accounts for its **weak** anti- inflammatory activity.
- Acetaminophen does not affect **platelet** function or increase blood clotting time.

Therapeutic uses

- Acetaminophen is a suitable **substitute** for the analgesic and antipyretic effects of aspirin for those patients with **gastric** complaints, those in whom prolongation of **bleeding** time would be a disadvantage, or those who do not require the anti-inflammatory action of aspirin.

- Acetaminophen is the analgesic/antipyretic of **choice** for **children** with viral infections or chickenpox (recall that aspirin increases the risk of **Reye's** syndrome).

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Pharmacokinetics

- Acetaminophen is rapidly **absorbed** from the GI tract. A significant first-pass metabolism occurs in the **luminal** cells of the intestine and in the **hepatocytes**.

- Under normal circumstances, acetaminophen is conjugated in the **liver** to form inactive metabolites.

- A portion of acetaminophen is hydroxylated to form **N - acetylbenzoiminoquinone** a highly reactive and potentially dangerous metabolite **that is toxic for liver cells.**

- At normal doses of acetaminophen, the N-acetylbenzoiminoquinone reacts with the sulfhydryl group of glutathione, forming a nontoxic substance.
  - ✓ **Overdose risk:** Excess acetaminophen can lead to accumulation of the toxic metabolite, so monitoring the dose is crucial.
  - ✓ Normally, adults take 500 mg per tablet, 1–2 tablets every 6 hours.
  - ✓ The maximum safe dose is 4 g/day (8 tablets of 500 mg).
  - ✓ Chronic or excessive use can easily exceed this limit, causing liver toxicity due to metabolite accumulation.
- Acetaminophen and its metabolites are excreted in the urine.

Adverse effects

- With normal therapeutic doses, acetaminophen is virtually free of any significant adverse effects .

- Renal tubular necrosis and hypoglycemic coma are rare complications of prolonged, large-dose therapy.

- large doses Hepatic necrosis, a very serious and potentially life-threatening condition can result.

  - Treatment: The antidote is acetylcysteine, which scavenges the toxic free radicals. This treatment is effective if given within 8–12 hours of acetaminophen overdose; after this window, signs of liver pathology or necrosis begin to appear.

- Renal tubular necrosis may also occur .

- Periodic monitoring of liver enzymes tests is recommended for those on high-dose acetaminophen.

Thank You

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:
(numbered in order as cited in the text)

1. Dr. Alia Recorded Lecture

Extra References for the Reader to Use:

1. Dr. Abdelmotaal Fouda
2. Dr. Matt (in 2 minutes)

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide 51 ; 1st Note	**from** the third prime minister	**In** the third trimester
V1 → V2	Slide 36 ; 2nd Note	**glycogenesns**	**gluconeogensis**