# Non-steroidal anti-inflammatory drugs

**At the end of the lecture the students should:**

- **Define NSAIDs**
- **Describe the classification of this group of drugs**
- **Describe the general mechanism of actions**
- **Define the following terms :**
  - **Analgesic**
  - **Antipyretics**
  - **Anti-inflammatory**
  - **Anti-platelet**
- **Describe the general pharmacological actions**
- **Describe the general therapeutic uses**
- **Describe the general adverse effects**
- **Describe the general contraindications**
- **Know some examples of each group of NSAIDs**
- **Know the difference between the selective & non-selective NSAIDs**

COX-1 is now known to be present in most tissues as the housekeeper enzyme. (COX-1 maintains the normal lining of the stomach. The enzyme is also involved in kidney and platelet function).

COX-2 is inducible by inflammation. It is not present at baseline, but increases in response to inflammation.

Both Cox-1 & 2 have the same affinity to convert arachidonic acid to prostaglandin. COX-1 maintains normal gastric mucosa and influences kidney function**. The inhibition of COX-1** is therefore **undesirable. The inhibition of COX-2** on the other-hand is a **desirable** effect as it appears to confer anti-inflammatory effects without inhibiting the prostaglandins that are important for normal physiologic function of the gastrointestinal, renal, and hemopoietic systems.

So Cox1 is related with PROSTAGLANDIN while Cox2 is NOT

**Cox: Cyclooxygenase**

**ANALGESIC: Drug that relieve pain.**

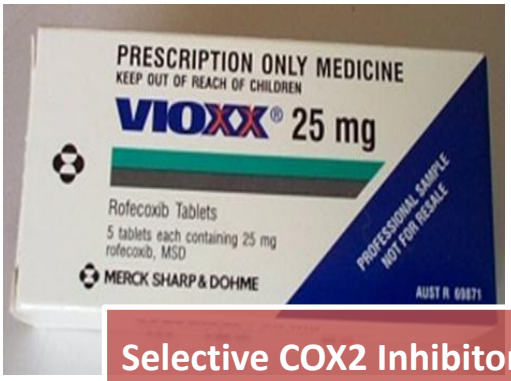
**Hypothermia: decrease the normal body temperature to below the normal.**

**ANTIPYRETIC: Drug that lower the elevated body temperature to normal. But, if we take it in normal temperature it won't affect. WHY? Because aspirin inhibit the synthesis of Prostaglandins which is the reason of the high temp.**

**NSAID: inhibit COX enzymes: inhibit prostaglandins senses.**

# CLASSIFICATION OF NSAIDs


**Non-Selective COXs Inhibitor**




**Selective COX2 Inhibitor**

- Non selective NSAID inhibit the synthesis of all types of prostaglandins.
- Selective NSAID will inhibit COX2 thus COX1 is still working(some prostaglandins are synthesized).
- Never take Non selective NSAID on an empty stomach because it will cause GIT bleeding and ulceration as a side effect
- While selective NSAID can be given on empty or full stomach
- Inhibition of uterine contraction of selective NSAID can be an advantage in dysmenorrhea and as a disadvantage in labor

# PHARMACOKINETIC

**Oral administration**

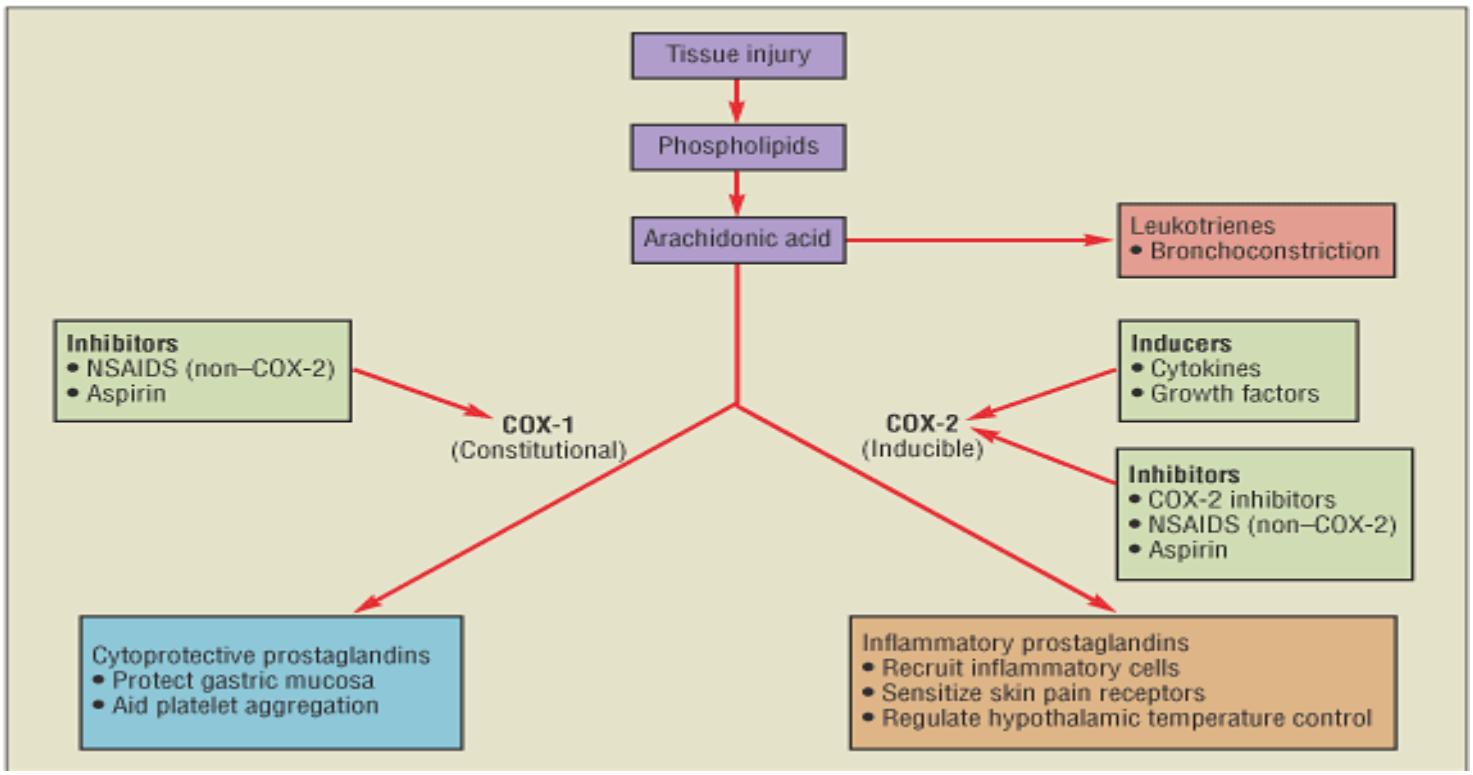
Most NSAIDs are weak acid (absorbed well in stomach and intestinal mucosa)

95% bound to plasma-protein (high bioavailability), so they can displace other drugs.

Most metabolized in liver (oxidation & conjugation)


Alkalization of urine using sodium bicarbonate $NaHCO_3$ increases excretion of acidic drugs like NSAID.

# MECHANISM OF ACTION OF N-NSAIDS:




## Aspirin is irreversibly inactivates cyclooxygenase enzymes.

**All NSAID drugs are reversibly inactive cyclooxygenase enzymes except Aspirin. Be careful, when patient use Aspirin, He should stop it 7 days before surgery because Aspirin is irreversibly effect on platelets, so the bleeding will be prolonged.**

| Analgesic | Antipyretic | Anti-Inflam | Effect on platelets |
|---|---|---|---|
| **Centrally** inhibition of COX enzymes in CNS **peripherally** Anti-Inflammatory action | **Centrally** inhibition of COX enzymes in CNS inhibition of interleukin-1 | **Peripherally** inhibition of COX enzymes Antioxidant effect | Inhibit platelet aggregation through inhibition the synthesis of TXA2 ( inhibit cox-1) |

**ACTIONS ON THE KIDNEY**:

- Salt & water retention may cause edema. (Inhibit synthesis of PGE2 & PGI2 that are Responsible for maintaining renal blood flow)
- Hyperkalemia.
- Interstitial nephritis (except aspirin).

**Using NSAIDs for long period of time, causes Kidney Failure.**

**RESPIRATORY ACTIONS (SPECIFIC FOR ASPIRIN):**

- Therapeutic doses aspirin elevates CO2 & increased respiration.
- High doses acts directly on the respiratory center resulting in Hyperventilation & respiratory alkalosis.
- Toxic doses , central respiratory paralysis & respiratory acidosis (Continued production of co2).

## THERAPEUTIC USES SHARED BY NS-NSAIDs:

- ❖ Antipyretic
- ❖ Analgesic (type of pain):
  Headache, migraine, dental pain
- ❖ Common cold.
- ❖ Rheumatic/rheumatoid arthritis/myositis
  Or other forms of inflammatory conditions.
- ❖ Dysmenorrhea

**This type of pain is mild, meditate or dull ache.**

**Rheumatoid Arthritis:**
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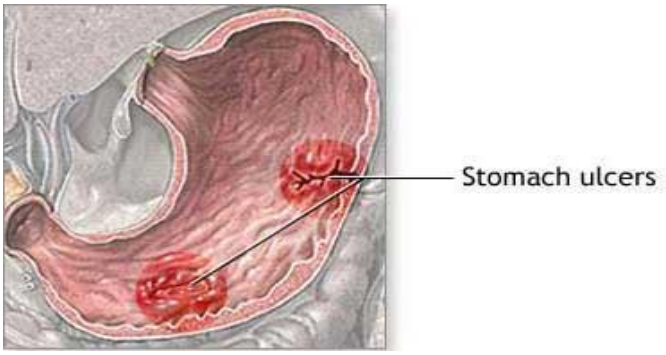
**The NSAIDs have harmful effect in the GIT, because they inhibit the production of prostacyclin which has protective effects in the GIT.**

**Some of Cytoprotective effects of the Prostacyclin:**
**1- Secretion of mucus.**
**2- decrease acids secretion**
**3- increase blood flow**

# ADVERSE EFFECTS SHARED BY N-NSAIDS:

- ❖ GIT upsets (nausea, vomiting).
- ❖ GIT bleeding & ulceration.
- ❖ Bleeding.
- ❖ Hypersensitivity reaction.
- ❖ Inhibition of uterine Contraction.
- ❖ Salt & water retention.





## Clinical Uses:

- Acute rheumatic fever.
- Low doses reduce the incidence of myocardial infarction & unstable angina (cardioprotective).
- Chronic gouty arthritis with large doses.
- Chronic use of small doses of aspirin reduces the incidence of colorectal cancer.

## External applications:

- Salicylic acid is used topically to treat corns.
- Methyl salicylate (oil of wintergreen) is used as counter irritant.

## Adverse Effects Related to:

| (A) Therapeutic Doses Of Aspirin | (B) LARGE doses or Chronic use of aspirin |
|---|---|
| -Nausea & vomiting | -Salicylism (ringing of ear "tinnitus", "vertigo" |
| -Hypersensitivity ( Aspirin asthma)** | -Hyperthermia |
| -Acute Gouty arthritis | Gastric ulceration & bleeding |
| -Reye's syndrome | -Respiratory depression & uncompensated respiratory & metabolic acidoses |

****Why Aspirin Asthma**

**Because the NSAIDs will inhibit Coxs pathways and doesn't inhibit Lipoxygenase so all the Arachidonic acid will be converted into Lipoxygenase pathway, some of the**

**- leukotrienes (which is Lipoxygenase) is potent bronchoconstrictor.**

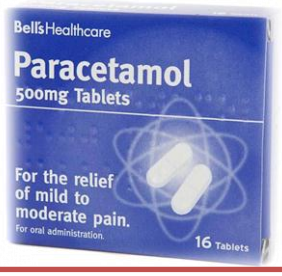
**Reye's syndrome**: The classic features are a rash, vomiting, and liver damage. The exact cause is unknown, and while it has been associated with aspirin consumption by children with viral illness.

## CONTRAINDICATIONS:


- Peptic Ulcer.
- Pregnancy.
- Hemophilic Patients.
- Patients Taking Anticoagulants.
- Children with Viral Infections.
- Gout (Small Doses).

****Teratogenic: Able to disturb the growth and development of an embryo or fetus.**

**Why we should not give the aspirin to the pregnant Women?**
**At the time of delivery the prostaglandin will make a contraction, so if the pregnant women used it the effect of the prostaglandin will be inhibited then the delivery will be delayed.**
**Inaddtion to that the aspirin has a teratogenic** effect and if it's used in the first trimester it can cause miscarriage.**




❖ **Is commonly used as analgesic antipyretic.**
❖ **Not used as anti-inflammatory drug**
❖ **Is safely used in patients suffering from :**

- ✓ Peptic or gastric ulcers.
- ✓ Bleeding tendency.
- ✓ Allergy to aspirin.
- ✓ Viral infections especially in children.
- ✓ Safely used during Pregnancy.

- Paracetamol mainly works on center COX and has no or weak effect on peripheral COX.

## Adverse Effects:

| Therapeutic doses | Large doses cause |
|---|---|
| elevate liver enzymes | liver & kidney necrosis |

**Treatment Of toxicity of paracetamol by (antidote):**
**N- acetylcysteine (SH- donor to neutralize the toxic metabolite).**

## Clinical uses

- Long-term use in treatment of rheumatoid arthritis, osteoarthritis & ankylosing spondylitis (accumulates in synovial fluid).
- Analgesic.
- Antipyretic.
- Acute gouty arthritis.
- Locally to prevent post-opthalmic inflammation.

## Preparations of Diclofenac:

- Diclofenac with misoprostol decreases upper gastrointestinal ulceration, but result in diarrhea.
- Diclofenac with omeprazole to prevent recurrent bleeding.
- .1% opthalmic preparation for postoperative opthalmic inflammation.
- A topical gel 3% for solar keratoses.
- Rectal suppository as analgesic.
- Oral mouth wash.
- Intramuscular preparations.

# Selective COX-2 inhibitors:

## General advantages:

- ❖ Potent anti-inflammatory
- ❖ Antipyretic & analgesic
- ❖ Lower incidence of gastric upset
- ❖ No effect on platelet aggregation (COX-1)

## General adverse effects:

- ❖ Renal toxicity (inhibition of PG synthesis)
- ❖ Dyspepsia & heartburn
- ❖ Allergy
- ❖ Increase incidence of myocardial infarction (Lack cardioprotective effect)

**Because they have no effect on COX-1, resulting in synthesis of thromboxane-2 that aggregates platelets & forming intravascular thrombosis.**

## GENERAL CLINICAL USES

**They are commonly used as anti-inflammatory drugs especially in patients suffering from any GIT problems such as peptic ulceration.**

- ❖ Rheumatoid arthritis.
- ❖ Osteoarthritis.
- ❖ Acute gouty arthritis.
- ❖ Acute musculoskeletal pain.
- ❖ Ankylosing spondylitis.
- ❖ Dysmenorrhea.
- ❖ They are recommended in postoperative patients undergoing bone repair (potent anti-inflammatory).
- ❖ Indicated in primary familial adenomatous polyposis (tumors, inflammatory reactions play important role in their pathology**).**

- ❖ **Half-life 11 hours ( taken twice /day)**
- ❖ **Food decrease its absorption**
- ❖ **Highly bound to plasma proteins**


## Clinical uses & adverse effects:

Discussed before with general used & general adverse effects.

## Drug interactions

With warfarin (anticoagulant drug )celecoxib potentiates its action through inhibiting its metabolism resulting in bleeding .

- Non peptic ulcer when use COX2 inhibitors because COX1 is still working thus there is still synthesis of prostaglandins.

Some useful videos:

http://www.youtube.com/watch?v=o1vjUC-volI

https://www.youtube.com/watch?v=018PxnH702k&feature=youtube_gdata_player