

**Pharmacology Team**

# **Non-steroidal anti-inflammatory drugs**

## **OBJECTIVE:**

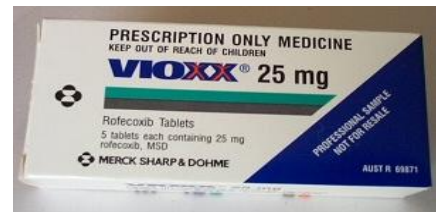
- **At the end of the lecture the students should :**
- **Define NSAIDs**
- **Describe the classification of this group of drugs**
- **Describe the general mechanism of actions**
- **Define the following terms :**
  - Analgesic**
  - Antipyretics**
  - Anti-inflammatory**
  - Anti-platelet**
- **Describe 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**

# CLASSIFICATION OF NSAIDS

## • Non-Selective COXs Inhibitor



## • Selective COX2 Inhibitor



Non-selective COXs inhibitor: inhibit COX-1 and COX-2.

Selective COX-2 Inhibitor: inhibit COX-2

(COX-1) is known to be present in most tissues” constitutive”. In the gastrointestinal tract, COX-1 maintains the normal lining of the stomach. The enzyme is also involved in kidney and platelet function.

Cyclooxygenase-2 (COX-2) is primarily present at sites of inflammation “inducible”.

(Both COX-1 and COX-2 convert arachidonic acid to prostaglandin)



✓ ARE GROUP OF DRUGS THAT SHARE IN COMMON THE CAPACITY TO INDUCE THE FOLLOWING ACTIONS :

- ANALGESIC
- ANTIPYRETIC
- ANTI-INFLAMMATORY
- ANTI-PLATELET
- ACTIONS ON THE KIDNEY

**Analgesic:** drug that relieve pain.

**Antipyretic:** drug that lower the elevated body temperature.



Drug reduces the body temperature when it is elevated. In normal temperature, it doesn't effect. WHY?

Because aspirin inhibit the synthesis of Prostaglandins which is the reason of the high temp.

## Pharmacokinetic

### Oral administration

- Most metabolized in liver (oxidation & conjugation)



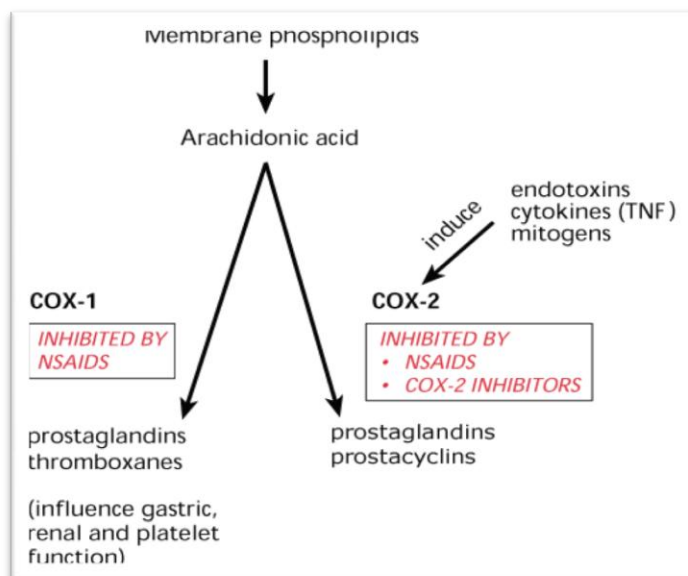
- Most NSAIDs are weak acid (absorbed well in stomach and intestinal mucosa)

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

Alkalinization of urine using sodium bicarbonate  $\text{NaHCO}_3$  increases excretion of acidic drugs like NSAID.



# MECHANISM OF ACTION OF N-NSAIDS

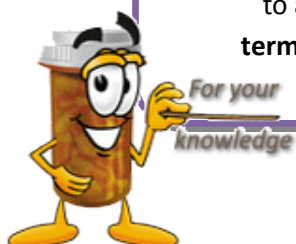


**(Aspirin is irreversibly inactivates cyclooxygenas enzymes)**

All NSAID drugs is reversibly inactive cyclooxygenas 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  |
|---|--|--|--|
| <ul style="list-style-type: none"> <li>• CENTRALLY INHIBITION OF COX ENZYMES IN CNS</li> <li>• PERIPHERALLY ANTI-INFLAMMATORY ACTION</li> </ul> | <ul style="list-style-type: none"> <li>• CENTRALLY inhibition of cox enzymes</li> <li>• In CNS</li> <li>• Inhibition of interleukin-1</li> </ul> | <ul style="list-style-type: none"> <li>• PERIPHERALLY INHIBITION OF COX ENZYMES</li> <li>• ANTIOXIDANT EFFECT</li> </ul> | <ul style="list-style-type: none"> <li>• INHIBIT PLATELET AGGREGATION THROUGH INHIBITION THE SYNTHESIS OF TXA<sub>2</sub> (INHIBIT COX-1)</li> </ul> |

An antioxidant is a molecule capable of inhibiting the oxidation of other molecules. Oxidation is a chemical reaction that transfers electrons or hydrogen from a substance to an oxidizing agent. Oxidation reactions can produce free radicals. **Antioxidants terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions.**



Centrally= in CNS  
Peripherally = in PNS

## ACTIONS ON THE KIDNEY:

- Salt & water retention & may cause edema  
(Inhibit synthesis of PGE<sub>2</sub> & PGI<sub>2</sub> that are responsible for maintaining renal blood flow)
- Hyperkalemia
- Interstitial nephritis ( except aspirin)

## RESPIRATORY ACTIONS (SPECIFIC FOR ASPIRIN):

- Therapeutic doses aspirin elevates CO<sub>2</sub> & 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 co<sub>2</sub>)

## ✓ 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

The types of pain: mild , moderate, dull ache .  
Dull ache= we can't explain this pain like HEADACHE. Not used in visceralpain

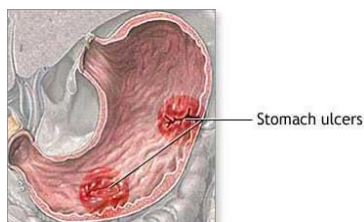
## ✓ ADVERSE EFFECTS SHARED BY N-NSAIDS

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

**WHY 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





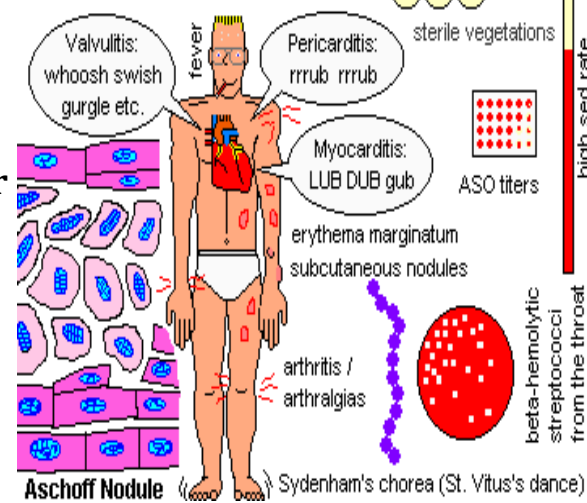
## Clinical Uses:

- 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.

### Acute Rheumatic Fever



### WHY?

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.



## Adverse Effects Related to

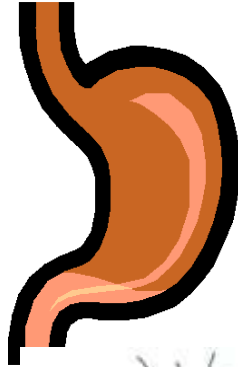
| (A) Therapeutic Doses Of Aspirin  | (B) LARGE doses or Chronic use of aspirin   |
|---|---|
| <ul style="list-style-type: none"> <li>• Nausea &amp; vomiting</li> <li>• Hypersensitivity ( Aspirin asthma)</li> <li>• Acute Gouty arthritis</li> <li>• Reye's syndrome</li> </ul> | <ul style="list-style-type: none"> <li>• Salicylism ( ringing of ear( tinnitus) , vertigo)</li> <li>• Hyperthermia</li> <li>• Gastric ulceration &amp; bleeding</li> <li>• Respiratory depression &amp; uncompensated respiratory &amp; metabolic acidoses</li> </ul> |

**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.





## ADVERSE EFFECTS RELATED TO HIGH DOSES



## CONTRAINDICATIONS

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

### 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.

In addition to that the aspirin has a teratogenic\* effect and if it's used in the first trimester it can cause miscarriage

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



# PARACETAMOL

- 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.**

## Adverse Effects:

Mainly on liver due to its active metabolite  
( N-acetyl-p-benzoquinone)

Doctor said it is not  
important to know the

- Therapeutic doses elevate liver enzymes
- Large doses cause liver & kidney necrosis
- Treatment Of toxicity of paracetamol by (antidote) :  
**N- acetylcysteine** ( SH- donor to neutralize the  
toxic metabolite

## DICLOFENAC:

### 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-ophthalmic inflammation.



### Preparations of Diclofenac:

- Oral preparation with or without misoprostol to decreases upper gastrointestinal ulceration .
- 0.1% ophthalmic preparation for postoperative ophthalmic inflammation.
- A topical gel
- Rectal suppository
- Oral mouth wash.
- Intramuscular preparation

## Selective COX-2 inhibitors

### ✓ General advantages :

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

### ✓ General adverse effects:

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

Why?

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),

**Example of selective COX-2 inhibitors  
(Celecoxib)**

- 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 .

# Summary:

- NSAIDs are group of drugs that have analgesic , antipyretic , anti-platelet & anti-inflammatory effects.
- They are classified according to their action on COX-enzymes into non-selective that inhibit both COX-1 & COX-2 & selective that inhibit only COX-2 enzymes.
- They are sharing in common therapeutic uses as analgesic to relief mild to moderate pain not visceral pain , reducing high body temperature, preventing clot formation , so aspirin can be used as prophylaxis in ischemic heart disease.
- As anti-inflammatory in rheumatic , rheumatoid arthritis, desmenrrhea and other inflammatory conditions including muscles or bones.
- The common adverse effects includes : gastric upset ( nausea, vomiting ,gastric ulceration or bleeding).
- Allergy
- Edema
- They are contraindicated mainly in patients with peptic ulcer , bleeding tendency or in pregnancy .
- Selective COX-2 inhibitors as celecoxib are potent anti-inflammatory & analgesic ,but have no anti-platelet effect & less gastric upset.
- They can be used in patients with gastric ulcer , haemophilia .
- Their common adverse is mainly on kidney & cardiovascular system.