

# Pharmacology Team

Our notes are in orange

و ننتبه للنوتات اللي بالبنفسجي لانها نوتات الدكتور بنفسها واكدت انها مهمه

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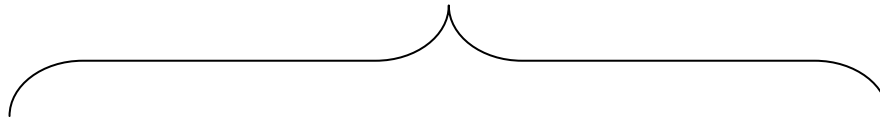
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# **NONSTEROIDAL ANTIINFLAMMATORY DRUGS**

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## NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAID's)



Non-selective

Selective

**Note:**

Prostaglandin → produced by 2 enzymes Xanthine oxidase<sub>1,2</sub> ( COX1 , COX2)

COX1 , COX2 Both inhibited by non-selective NSAIDS

COX2 inhibited by the selective NSADIS

### NONSELECTIVE Group (NNSAIDs)

- **ASPIRIN**

( Acetyl Salicylic Acid ) and is the Prototype of nonselective NSAIDs

### Pharmacological Actions Of NNSAIDs

- **1- Anti-inflammatory**

a . Inhibition of prostaglandin synthesis through inhibition of COX enzymes ( COX-1&COX-2). **Inhibit both enzymes**

b. Inhibit the synthesis of kinins ( chemical mediators of the Kallikrein system ). **Inhibit the inflammatory mediators**

c. Stabilization **stops** of lysosomes **which, damages tissues**

d. Block the migration of Polymorphnuclear leukocytes to the site of inflammation ( inhibition of chemotaxis ).

e. Anti-oxidant activity **blocks free radicals by engulfing them**

**Note:**

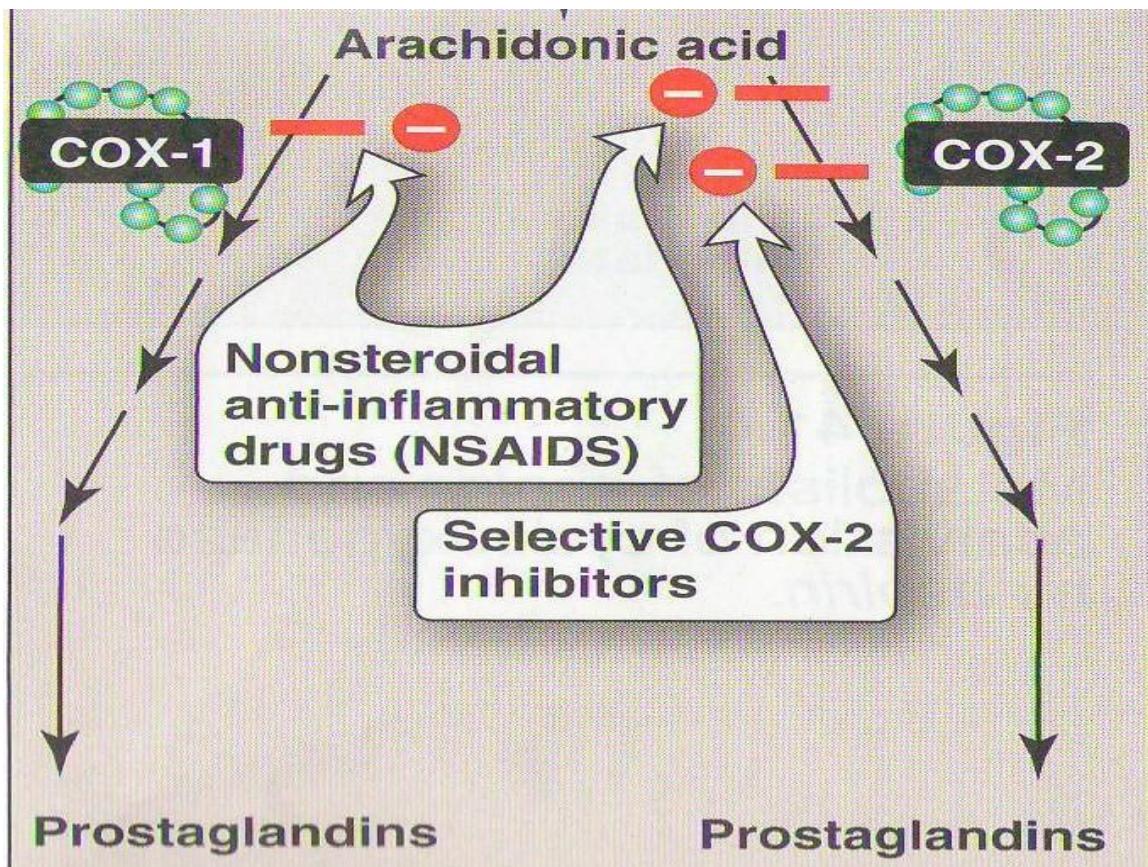
**Difference b/w**

**COX1**

This enzyme produce types of prostaglandin important for the GIT

**COX2**

This enzyme is expressed in kidney bone and brain  
It is elevated in inflammation



**NOTE:**  
**ASPIRIN is IRREVERSIBLE**  
**INHIBITOR TO COX ENZYMES**

## **2- Analgesic Effects**

- Anti-inflammatory effect **when reducing the inflammation we are reducing the pain**
- Inhibition of COX enzymes in the CNS **inhibit the prostaglandin produced by CNS**
- ( Inhibits the synthesis PGE<sub>2</sub> ) type of prostaglandin

## **3- Antipyretic Effects**

**Note:**

**Hypothermia → reduces normal body temperature**

**Antipyretic → reduces high fever to normal**

**Through COX-2 inhibition in the CNS.**

**COX-2 is the dominant source of prostaglandins that mediates rise in temperature.**

Prostaglandin causes fever by triggering hypothalamus and elevates heat production so NSAID's causes vasodilatation and loss of heat → increase sweating promote further decrease in body temperature

## **4- Antiplatelet Effects**

- Inhibits platelet COX-1 enzyme

**Inhibits TXA<sub>2</sub> " thromboxane A<sub>2</sub> " production. Which is responsible for platelet aggregation**

**Antiplatelet effect of aspirin lasts 8-10 days**

Aspirin inhibits enzyme **irreversibly** → lasts long time ( 8 – 10 ) days

**Clinical importance :** cessation of aspirin before doing operation from 8 – 10 days to prevent surgical bleeding

**Note:  
ADMINISTRATION OF ASPIRIN  
SHOULD BE STOPPED AT  
LEAST  
7-10 DAYS BEFORE ANY  
SURGICAL OPERATION**

## **5- Gastrointestinal Effects**

- Inhibits PGE<sub>2</sub> , PGI<sub>2</sub> resulting in gastric upset up to gastric ulceration & bleeding

COX1 → responsible for the synthesis of many important prostaglandin that protect GIT by :

- Reducing gastric secretion ↓
- increasing gastric blood flow
- Protection of mucus layers

NSAID's inhibits COX1 this will lead to vomiting and gastric irritation

That's why Aspirin must be taken with meals or shortly after eating, and patient strongly advised to drink water

**Note:  
NSAIDs SHOULD BE TAKEN AFTER  
MEALS & PATIENTS ARE ADVISED  
TO DRINK WATER**

## **6-Effects on Kidney ( MCQ )**

- Inhibition of prostaglandins – mediated renal functions ( PGE<sub>2</sub> & PGI<sub>2</sub> ) resulting in salt & water retention , hyperkalemia , interstitial nephritis

This Side Effect Can Reduce Effectiveness of Antihypertensive (HT) agents

COX2 enzyme → prostaglandin important for maintain normal kidney function

Aspirin → reduce HT drugs effect because it result in salt and water retention

## 7- Respiratory Effects especially for aspirin

- Therapeutic doses increase oxygen consumption & CO<sub>2</sub> production. The increased CO<sub>2</sub> production stimulates respiration.
- Toxic doses cause central respiratory paralysis & respiratory failure.

**Note:**  
**Respiratory effects related to  
aspirin only**

### Clinical uses shared by NSAIDs

- ANALGESIA

Migraine, Headache, Dental pain , Dysmenorrhea > painful menstruation

- NSAIDs USED ONLY FOR MILD TO MODERATE PAIN , NOT EFFECTIVE FOR VISCERAL PAIN
- ANTIINFLAMMATORY

Treatment of musculoskeletal disorders as rheumatoid arthritis, Myositis & osteoarthritis

They provide only symptomatic relief from pain & inflammation

They do not arrest the progression of pathological injury to tissues.

#### NOTE

- All NSAIDs selective or non selective except aspirin are used in the treatment of acute gouty arthritis

Antipyretic

- Reduce fever in most situations

## NOTE

- All NSAIDs, including selective COX-2 inhibitors are analgesic , antipyretic & anti-inflammatory, with the exception of acetaminophen, which is analgesic & antipyretic only

## Clinical uses of aspirin

- Antithrombotic ( Cardioprotective)
- Chronic gout ( Large doses ) **because it takes time till it give its effect**
- Cancer chemoprevention ( Reduces the incidence of cancer colon )

## Adverse Effects shared by NNSAIDs

- Gastrointestinal upset including ulceration & bleeding
- Blockade of platelet aggregation
- Inhibition of uterine motility ( prolong labor)
- Renal adverse effects
- Hypersensitivity reactions

## Adverse Effects related to Therapeutic Doses of aspirin

- Acute Gouty arthritis
- Reye's Syndrome ( cerebral edema , hepatic failure )" fever of viral infection affect patient ↓ 20 years "

## Adverse Effects Related to High & Toxic Doses

- Salicylism " **tinnitus** **طنين** ", **reversible by reducing the dosage**
- Metabolic acidosis
- Hyperthermia **over production of heat**
- Gastric ulceration & bleeding



## Contraindications Of NSAIDs

- Pregnancy
- Hemophilic patients
- Peptic ulcer

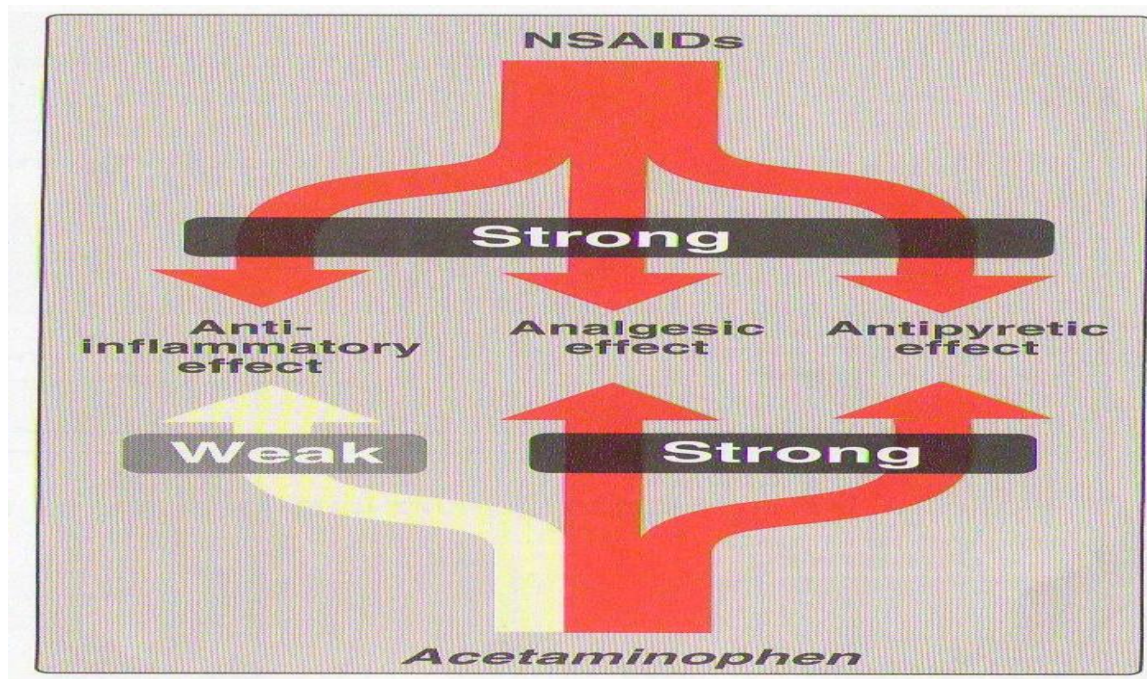
**ASPIRIN IS CONTRAINDICATED  
IN VIRAL INFECTIONS MAINLY  
IN  
CHILDREN**

## Paracetamol ( Acetaminophen )

- Effective as analgesic & antipyretic **only**
- Has **neither** antiinflammatory **nor** antiplatelet **(MCQ)**

## Can be used in : **(MCQ)**

- pregnancy
- Patients allergic to aspirin
- Children with viral infections
- Patients with hemophilia or peptic ulcer



## Adverse Effects (MCQ)

- Mainly on liver due to its active metabolite  
Therapeutic doses elevate liver enzymes
- High doses cause liver & renal necrosis

DICLOFENAC "voltaren"

## Pharmacokinetics

- Accumulates in synovial fluid .

## Preparations:

- Oral tablets With misoprostol
- .1% ophthalmic preparation to prevent postoperative ophthalmic inflammation
- Topical gel for solar keratoses
- Rectal suppository as analgesic or for postoperative pain

- Oral mouth wash
- Intramuscular preparations

## Clinical uses

- Antiinflammatory , Analgesic , Antipyretic
- Acute gouty arthritis
- Locally to treat or prevent postophthalmic inflammation.
- Topical for solar keratoses

## Adverse effects

Same as General adverse effects of NSAIDs

## Selective COX-2 inhibitors

- **General Advantages :**
- Potent antiinflammatory drugs
- Antipyretic & analgesic
- Lower incidence of gastric upset
- No effect on platelet aggregation ( COX-1)

## General Clinical uses

- Short – term use in Postoperative patients
- Acute gouty arthritis
- Acute musculoskeletal pain
- Ankylosing spondylitis **an inflammatory reaction in the vertebral column**

## General Adverse effects

- Renal toxicity
- Dyspepsia & heartburn
- Allergy
- Cardiovascular ( do not offer the cardioprotective effects of nonselective NSAIDs )

## Celecoxib

- Half-life 11 hours
- Given twice daily
- Food decreases its absorption
- Highly bounded to plasma proteins