PHARMACOLOGY
TEAM 439

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MED439
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Editing file

# NSAIDs

Lecture 2

## OBJECTIVES:

- To focus on the general mechanism of action of NSAIDs.
- To outline the common pharmacodynamic effects and ADRs of NSAIDs.
- To classify NSAIDs on basis of their specificity to COX enzyme.
- To detail on the pharmacokinetic properties and pharmacodynamic effects of selected NSAID

Important

In male and female slides

Only in male slides

Only in female slides

Extra information

Helpful video

# NSAIDs Epidemiology

**1-** NSAIDs account for 3.8% of all prescriptions.
**2-** A significant quantity is sold over the counter (OTC).
**3-** Use increases with age
**4-** 90% of all NSAIDs prescriptions are issued to patients at ages over 65 years.
**5-** NSAIDs is the most prominent risk for gastric ulceration, hemorrhage and perforation.
**6-** The prevalence of NSAIDs-induced ulcers is 10% -30%

## NSAIDS effects

### 1- Anti-inflammatory

The 5-Ht , histamine,bradykinin, and inflammatory factors will stimulate the PG which will cause symptoms of inflammation : pain,redness,hot,swelling

**NSAIDs anti-inflammatory mechanism:**
Block PGs production at

**Site of action:** peripheral tissues

**Clinical uses:**
· Rheumatoid arthritis / Myositis* inflammation and degeneration of muscle tissue.
· Common cold

### 2- Analgesic (pain killer)

The bradykinin, histamine and the inflammatory factors will stimulate the PG that stimulates the nociceptive nerve endings and causing **pain**

**NSAIDs analgesics mechanism:**
block PGs production.
**Site of action:**
peripheral tissue.

**Clinical uses:**
· Headache, Migraine (headache that affects one side of the head
· Dysmenorrhea (Painful menstruation and abdominal cramps)
· Dental pain (moderate pain)

### 3- Antipyretic (reduce fever)

Pyrogens ( microbes) and inflammatory factors stimulate formation of Prostaglandins, which then increase the set point of the thermoregulatory center in the brain. This leads to ↑ heat production and ↓ heat dissipation (loss), resulting in **FEVER**.

**NSAIDs antipyretics mechanism:**
block PGs production

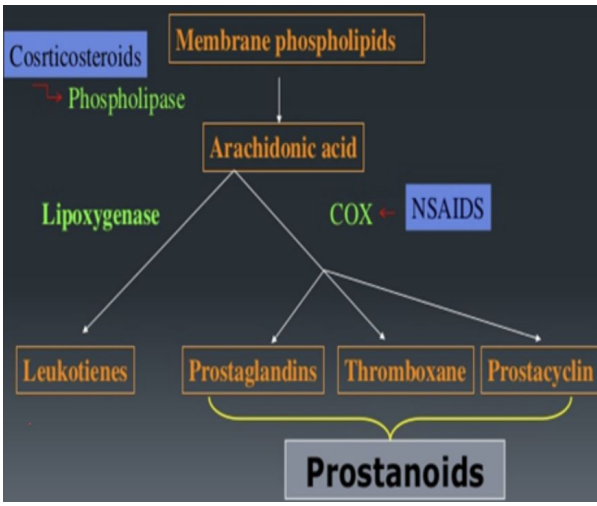
**Site of action:** CNS

**Clinical uses:**
Reducing fever back to normal body temperature.

# Mechanism of action of NSAIDs

**NSAIDs Inhibit CycloOxygenase enzyme (COX) which leads to the inhibition of Prostanoids synthesis.** Two enzymes act upon arachidonic acid (COX and lipoxygenase).

**Pharma 438:** Prostanoids promote inflammation, pain and fever. As a consequence, ongoing inflammation, pain and fever are reduced = all actions and side effects are due to this inhibition. **(Corticosteroids inhibit phospholipase A2 and the formation of arachidonic acid which produces prostanoids).**




**This diagram is very very important to understand the lecture. Make sure you study and understand it well**

## Classification of NSAIDs

### COX 1 "constitutive"

**Constitutive Homeostatic functions:** GIT, Renal tract, platelet function, macrophages differentiation.

**Normal Function :**

**1-** Protects the mucosal lining of the stomach
**2-** Supports blood clotting function of platelets.

**After taking NSAIDs which inhibit COX 1:**

They can cause ulcers in the stomach and promote bleeding. "Undesirable effect"

### COX 3

Found in the **brain of animals only.**

### COX 2 "Induced"

**Induced Inflammation:** Activated by IL-1, TNF, Inhibited by IL-4, glucocorticoids.

**Normal Function :**

Causes inflammation and pain

**After taking NSAIDs which inhibit COX 2:**

Pain and inflammation will be reduced "desirable effect"

# Classification of COX inhibitors:

| Type | Example |
|---|---|
| **Nonselective** (inhibits COX1 and COX2) | Aspirin , diclofenac , ibuprofen , ketoprofen , naproxen , piroxicam . Indomethacin |
| **Selective COX 2** (inhibits COX 2 only) (newer has more efficacy and less side effects) | Celecoxib . Etoricoxib , parecoxib, Lumiracoxib , Rofecoxib, valdecoxib |
| **Preferential COX 2 inhibitors** (Prefers inhibiting COX 2 more than COX 1) | Meloxicam |
| **COX 3 inhibitors** | Paracetamol |

# ADRs (Adverse drug reactions):

**1- GIT upset:**
nausea vomiting
Ulceration and bleeding
(It blocks the Constitutive PG that is responsible for GIT protection)

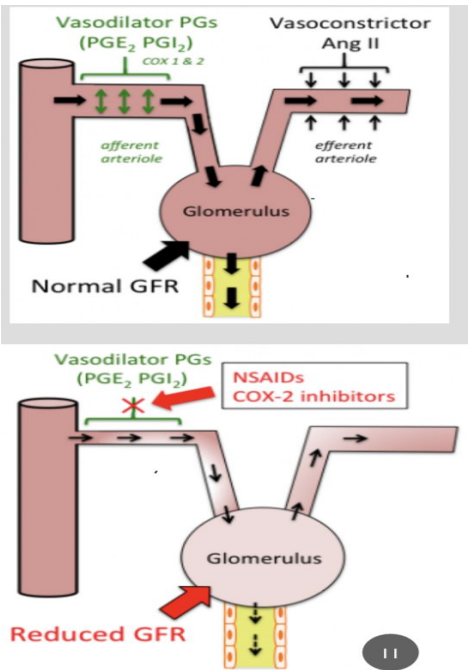
**2- Inhibition of uterine contraction** constitutive PG induce labor by contraction which is blocked **Not** advised during pregnancy

**3- Hypersensitive reaction** (develop rash and allergy ) due to genetic factors,immune system,idiosyncratic

**4- Impairment kidney function ,NSAIDs cause hemodynamically-mediated acute renal failure** (constitute COX1 synthesize the PGE2+PGI2 that vasodilate renal tubules leading to enhance GFR). NSAIDs inhibit the COX1 and cause vasoconstriction leading to the prevention of vasodilation and reducing GFR

**5- Salt & water retention**
Decrease excretion due to reduce GFR

**NOTES:**
- The most NSAID with the most severe ADRS is **indomethacin** (Non selective).
**- Rofecoxib and valdecoxib** (Selective) may cause myocardial infarction so they are withdrawn or out of market. The risk is caused because they have very high potency



# Non selective cox 1,2 inhibitors

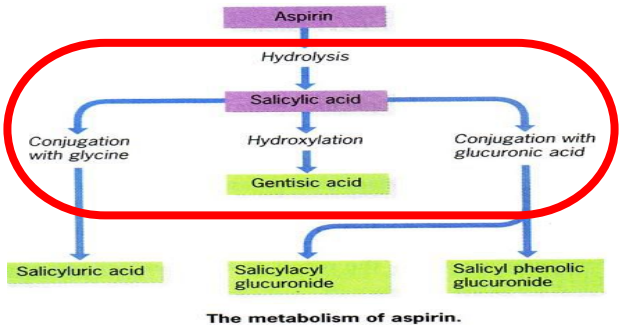
## Aspirin (Acetylsalicylate)

### Mechanism of action

-Aspirin binds with the active site of COX enzyme and makes it inactive. This process is irreversible. All NSAIDs bind reversibly except aspirin

### Pharmacokinetics

- Higher dose of aspirin has a long plasma half- life. Why?
  Aspirin follows Zero-Order kinetics, Meaning that the rate of elimination is constant regardless of the concentration
- small dose of aspirin cause retention of uric acid, while the high dose causes Increase in uric acid excretion.
- Difference in plasma Half life of Higher And lower dose is:
  Higher dose: t1/2 = 15h.
  Low dose: t1/2 = 3h.



The metabolism of aspirin.

when aspirin gets hydrolyzed to **salicylic acid,** it will have 3 fates which are;

1. conjugation with glycine
2. Conjugation with glucuronic acid
3. hydroxylation

### Clinical uses

- Acute rheumatic fever.
- Reduces the risk of myocardial infarction (cardioprotective). Inhibition of thrombosis formation. They prevent platelet COX 1, inhibiting TBA2 formation which is essential for platelet aggregation
- Prevention of pre-eclampsia (disorder of pregnancy) تعسر في الحمل
- Chronic use of small doses reduce the incidence of colon cancer.

### Contraindications:

**1-** Peptic ulcer **2-**pregnancy **3-**Hemophilia **4-** asthma **5-** gout (at small dose)
**6-** Patients taking anticoagulant , it may cause excessive bleeding.
**7-** Children with viral infections (Reye's syndrome)

### Clinical dose (adverse effects)

**1-** Hypersensitivity **2-** acute gouty arthritis due to uric acid retention
**3-**reye's syndrome Affects children with viral infection who take aspirin. **4-** Impaired haemostasis. Bleeding
**5-** GIT side effects, dyspepsia, nausea and vomiting
**6-** Mucosal damage → hemorrhage **7-** Bronchospasm in aspirin- sensitive asthmatics

### Overdose (adverse effects)

Hyperthermia, Gastric ulceration, bleeding, and salicylism (Ringing of ear, vertigo)

# Non selective cox 1,2 inhibitors

## Diclofenac (voltaren)

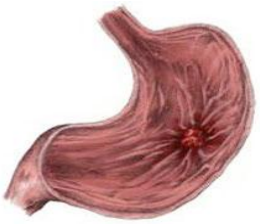
### Mechanism of action

- It does nonselective COX-2 Inhibition and it has activity for both COX-1 and COX-2 but increased affinity for COX-2

### Clinical uses

- Analgesic, antipyretic, anti inflammatory, and acute gouty arthritis. Usually used in combination with other drugs to control its ADRs (misoprostol which prevents and treats peptic ulcers, Omeprazole which prevents upper GIT bleeding)
- Used locally to prevent postoperative ophthalmic inflammation (solution). e.g(eye drops)
  for treating inflammation after operations on the eye. ophthalmic= related to the eye.

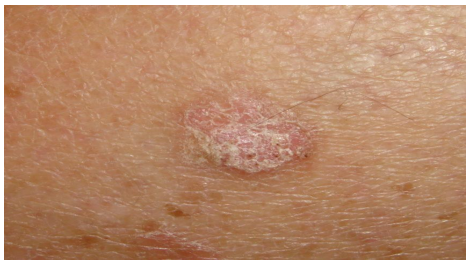
### Preparation:



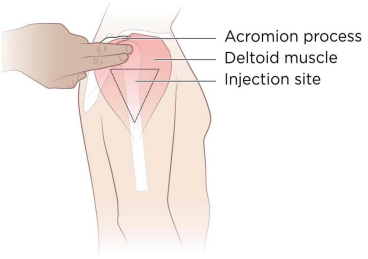
**1- Diclofenac with misoprostol** (a PGE 1 analog) it decreases upper GIT ulceration, but results in diarrhea

**2- Diclofenac with omeprazole** to prevent peptic ulceration, and recurrent bleeding.

**3- 0.1% ophthalmic preparation for** postoperative ophthalmic inflammation.



**4- A topical gel 3% for solar keratosis,** which is a common skin condition resulting from skin damaged by the sun for many years




**5- Oral mouth wash**
**6- Intramuscular Preparations**
**7- Rectal suppository** as analgesic

# Selective COX 2 inhibitors (coxibs)

## Coxibs

### Action

- Potent anti-inflammatory.
- Antipyretic & analgesic.
- Lower incidence of gastric upset.
- it has Lower harmful effects on stomach than non-selective inhibitors.

### General ADRs

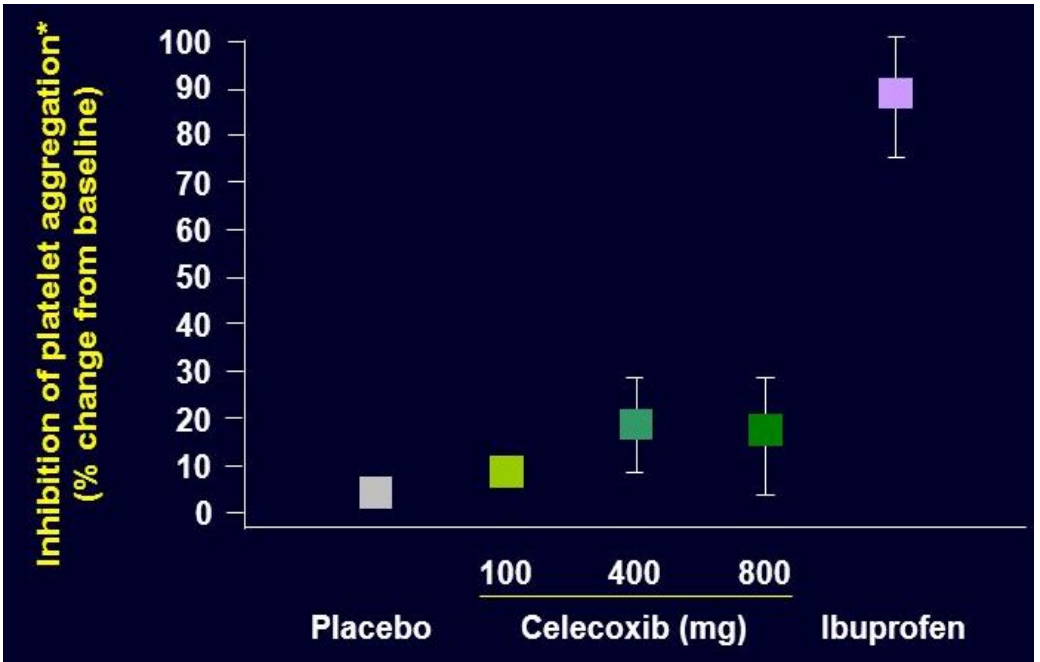
- Allergy
- Dyspepsia & heartburn (it is not as potent as the one caused by COX-1 inhibitors).
- Renal toxicity
- Cardiovascular, (do not offer the cardioprotective effects of nonselective group (not anti-platelet) COX-2 is found only in endothelial cells where Prostacyclin is found and Thromboxane is NOT found.)

### Clinical uses

- Short-term use in postoperative patients (to ↓ inflammation and ↑ body temperature.)
- Acute gouty arthritis
- Acute musculoskeletal pain
- Ankylosing spondylitis(inflammation of vertebrae which causes severe pain)

### Contraindications:

Any selective COX 2 inhibitor should **not** be prescribed to a patient with cardiovascular problems..




The graph on the left indicates that **Ibuprofen** (non-selective) produces effects on platelet aggregation(cox1) while **celecoxib(selective)** does not have an effect on it. نقدر نقول ان عنده تاثير بسيط جدا

# Cox 3 inhibitors

## Paracetamol

### General features

- Antipyretic
- Analgesic
- Weak anti inflammatory effect
- Given orally , well absorbed
- Metabolized by conjugation at therapeutic doses
- $t^{1}/_{2}$ =2-4 h
- COX-3 selective inhibitor.
- Binding of paracetamol to COX is **inhibited** by peroxides produced in inflammatory sites.

Extra info (**not required**):
Both Dr.Osama and Dr,ishfaq told me that Paracetamol is primarily considered a COX-3 inhibitor but just like how selective COX-2 inhibitors have a small effect on COX-1, Paracetamol inhibits COX-1 in humans since humans don't have COX-3. And it inhibits it poorly, hence it has no anti inflammatory effect(due to peroxides as mentioned)
-Homoud

### Clinical uses

Commonly used analgesic antipyretic instead of aspirin in cases of:

- Peptic or gastric ulcers
- Pregnancy
- Viral infections in children
- Bleeding tendency
- Allergy to aspirin

Why do we prefer using paracetamol instead of aspirin?
In order to achieve less severe contraindications.

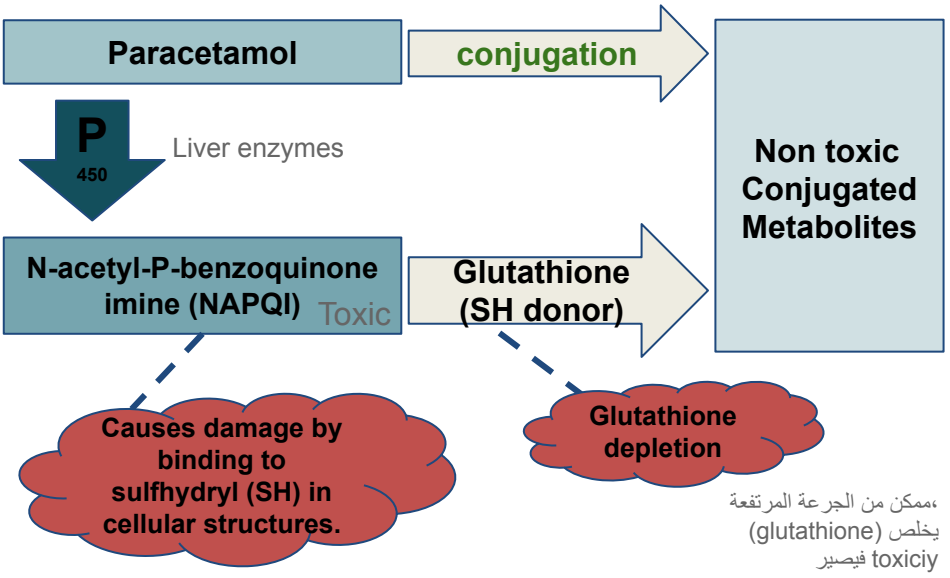
### ADRs

**Adverse Drug reactions**

**Therapeutic doses**
Elevate liver enzymes, No significant ADR.

**Large doses**
it is metabolized into N Acetyl-p-benzoquinone imine, which causes liver damage.

**Chronic abuse**
Nephrotoxicity




Treatment of toxicity or overdose of paracetamol is by N- acetylcysteine.

Uses of N- acetylcysteine:

- Children who accidentally take paracetamol without parental guidance.
- Intended overdose of paracetamol for suicidal purposes.

# Celecoxib (Selective COX 2 inhibitors)

is a type of Selective COX-2 inhibitors that is a derivative of sulphonamide and it acts mainly on Cox-2 and have little to no effect on Cox-1.

- $t^{1}/_{2}$= 11 hours.
- Food decreases its absorption (shouldn't be given with food).
- Highly bound to plasma proteins.
- Used for Ankylosing spondylitis and arthritis.
- it is contraindicated in patients who are allergic to sulfonamides.

## **Meloxicam** (Nimesulide , nambumetone ) **(Preferential COX 2 inhibitors)**

Is a type of preferential COX-2 inhibitors are a which inhibit COX-2 Slightly more than they inhibit COX-1.

- $t^{1}/_{2}$=20 hours
- it is preferable to use them in low doses due to preventing loss of selectivity.
- It becomes non selective in the case of an overdose
- Used for Osteoarthritis and rheumatoid arthritis.
- Associated with lower GIT symptoms compared to non-selective(COX) inhibitors .

More damage ← → Less damage

Non selective, preferential COX-2 inhibitor, Selective COX-2 inhibitors

# NOTES :

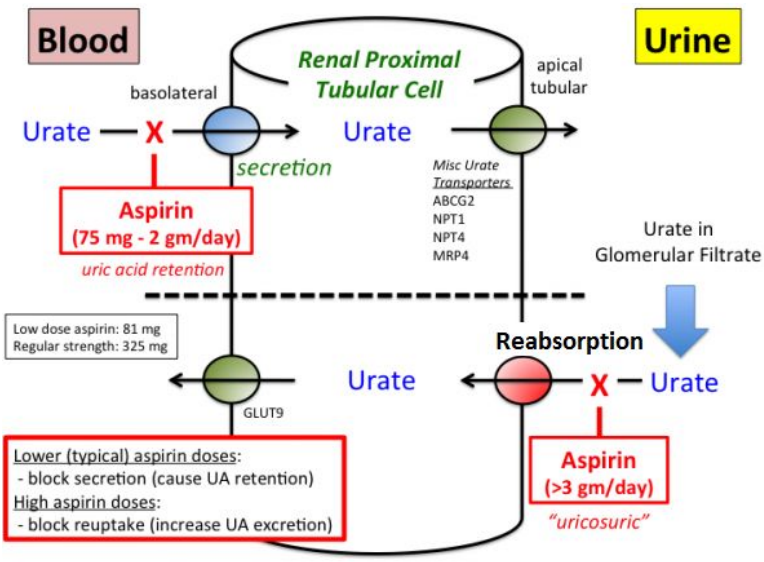
NSAIDs prevent production of prostanoids.

-Nonselective NSAIDs have an effect on thromboxane and prostacyclin.

-Selective NSAIDs (Coxibs) have an effect on prostacyclin only.

**Thromboxane** is in charge of vasoconstriction and activates platelets aggregation.
Nonselective drugs will prevent production of thromboxane (PG) -> no clot formation.

**Prostacyclin i**s in charge of vasodilation and inhibition of platelet aggregation (its job is opp to thromboxane) . Nonselective NSAIDs and Coxibs will prevent the prostacyclin from doing its job.




This figure shows why **gout** is a contraindication for aspirin **at low doses**
Will be accumulating of uric acid

# MCQ

MQ team made some Questions for you to solve!! **Check them out here**

| 1- Which of the following enzymes mediates inflammation? | | | |
|---|---|---|---|
| A- COX 1 | B- COX 2 | C- COX 3 | D- Lipoxygenase |

| 2- Which drug inhibits enzymes irreversibly? | | | |
|---|---|---|---|
| A-Diclofenac | B- Paracetamol | C- Aspirin | D- Celecoxib |

| 3- What NSAID effect is used to treat Dysmenorrhea (Painful menstruation)? | | | |
|---|---|---|---|
| A- Antipyretic | B- Analgesic | C- Anti-ulcer | D- Anti-inflammatory |

| 4- What may cause myocardial infarction as one of it's ADRs? | | | |
|---|---|---|---|
| A- Aspirin | B- Ibuprofen | C- Celecoxib | D- Valdecoxib |

| 5- If a child has Reye's syndrome, then which NSAID should be avoided ? | | | |
|---|---|---|---|
| A- Aspirin | B- Diclofenac | C- Paracetamol | D- Meloxicam |

| 6- Which one of the COX isoforms is found in the brain? | | | |
|---|---|---|---|
| A- COX 3 | COX 2 | COX 1 | IL-4 |

| 7- Which drug shouldn't be given to a patient if he/she is allergic to sulfonamides? | | | |
|---|---|---|---|
| A- Paracetamol | B- Indomethacin | C- Nimesulide | D- Celecoxib |

| 8- Meloxicam is an example of which type of inhibitors? | | | |
|---|---|---|---|
| A- Selective COX 2 | B- Preferential COX 2 | C- COX 3 | D- Non selective |

## ANSWERS

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|
| B | C | B | D | A | A | D | B |

# SAQ

1) What are the 3 effects of NSAIDs?

2) Describe the mechanism of action for NSAIDs

3) a 34 year old patient came to the hospital suffering from swelling of the eye accompanied by severe pain, he/she also performed an ophthalmic surgery a month ago. What NSAID should we prescribe to the patient?

4) What is the difference between a low dose and a high dose of aspirin?

5) A 65 year old man came to the hospital complaining from a pain in his joint that limits his movement, after examination the diagnosis is rheumatoid arthritis. What drug is suitable to prescribe to his condition?

6) List 3 Contraindications of taking aspirin.

7) A 66 year old man came to the hospital suffering from musculoskeletal back pain. He took paracetamol but it didn't help and he also has a medical history of gastric ulcer and hemophilia. What drug should we give to him?

8) What medication should we give a patient if he/she is overdosed with paracetamol?

## ANSWERS

A1) Anti-inflammatory, analgesic, and antipyretic.

A2) They Inhibit CycloOxygenase enzyme (COX) which leads to the inhibition of Prostanoids synthesis.

A3) Diclofenac

A4) small dose of aspirin cause retention of uric acid and has a half life of 3 hours, while the high dose causes an Increase in uric acid excretion. And has a half life of 15 hours.

A5) Meloxicam

A6) Peptic ulcer, pregnancy, and hemophilia.

A7) Celecoxib

A8) n-acetylcysteine

# GOOD LUCK!


## Team leaders

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## Girls team members

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شادن العبيد
سديم آل زايد
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ميس العجمي
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