Non-steroidal anti-inflammatory drugs (NSAIDs)

Inflammation => Signs and stimulus to a foreign material enter the body.

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Definition

- NSAIDs are class of drugs having the capacity to suppress the signs and symptoms of inflammation (anti-inflammatory effect).

- They also exert analgesic (Pain Killer مسكّن للألم) and anti-pyretic (Pirexi خافض للحرارة) effects.
  (Inflammation وهو أحد أعراض / "Suppress Fever")

- Therefore, these drugs are mainly indicated to relief pain, swelling, redness and stiffness caused by inflammation. (either chronic or acute or sudden diseases.)

Inflammation

- Inflammation is the body response to an injurious stimulus (*e.g.,* infections, chemicals, or physical injuries)
- Inflammation is triggered by release of chemical mediators from injured tissues and migrating cells such as WBC.
- These chemical mediators are histamine, bradykinin, interleukins and the most important are EICOSANOIDS such as prostaglandines and leukotrienes

لزيادة الفهم فقط:

Bradykinin: is **a potent endothelium-dependent vasodilator and mild diuretic**, which may cause a lowering of the blood pressure + pain mediator.

Interleukin (IL): any of a group of naturally occurring proteins that mediate communication between cells.
Interleukins **regulate cell growth, differentiation, and motility**.

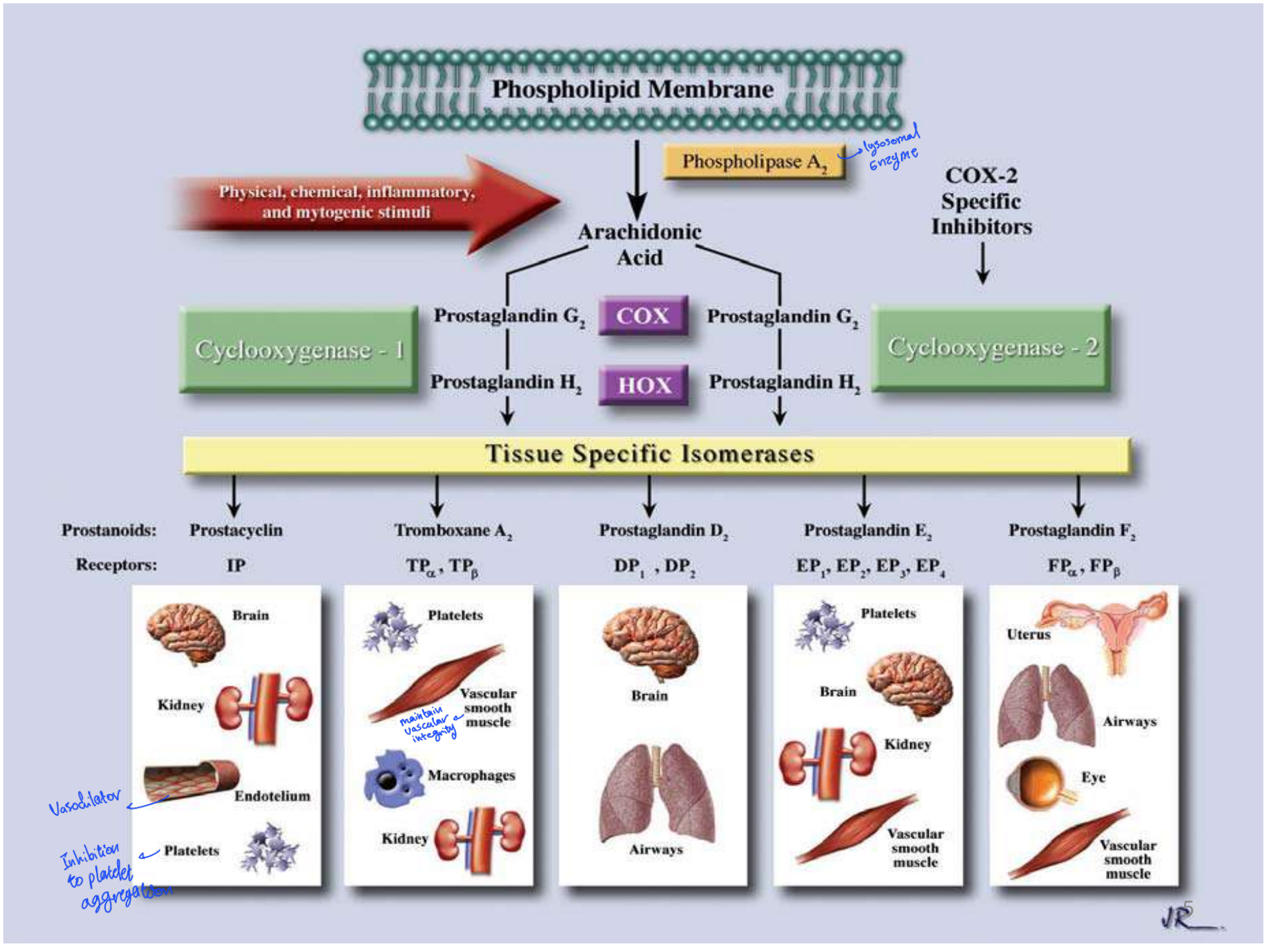
Eicosanoids: are **signaling molecules made by the enzymatic or non-enzymatic oxidation of arachidonic acid**

Prostaglandines (PGs)

- PGs are fatty acid derivatives produced by all tissues

- PGs act locally on the site of synthesis where they rapidly metabolized to inactive products.

- On the cell damage, PGs are formed from the primary precursor Arachidonic acid (AA) by enzymes called Cyclooxygenases (Cox)


Phospholipid Membrane
Phospholipase A2
lysosomal enzyme
Physical, chemical, inflammatory, and mytogenic stimuli
Arachidonic Acid
COX-2 Specific Inhibitors
Cyclooxygenase - 1
Prostaglandin G2
COX
Prostaglandin G2
Cyclooxygenase - 2
Prostaglandin H2
HOX
Prostaglandin H2
Tissue Specific Isomerases
Prostanoids:
Receptors:
Prostacyclin
IP
Tromboxane A2
TPα, TPβ
Prostaglandin D2
DP1 , DP2
Prostaglandin E2
EP1, EP2, EP3, EP4
Prostaglandin F2
FPα, FPβ
Brain
Kidney
Endotelium
Platelets
Vasodilator
Inhibition to platelet aggregation
Platelets
Vascular smooth muscle
maintain vascular integrity
Macrophages
Kidney
Brain
Airways
Platelets
Brain
Kidney
Vascular smooth muscle
Uterus
Airways
Eye
Vascular smooth muscle

- Under various stimuli, AA is liberated from phospholipids of cell membranes by the action of lysosomal enzymes (Phospholipase A2)

- AA is then oxidized by COX leading to formation of PGs (e.g. PGD_2 , PGE_2, PGF_{2a}), Thromboxanes (TX) e.g. TX A_2, and Prostacycline (PG I_2).

- There are two isoforms of Cox:

1. Cox-1
2. Cox-2

Cox-1

Big Boss J.

- Cox-1 is considered a house keeping enzyme, constitutively expressed in most tissues throughout body
- it catalyzes the formation of PGs involved in continuous regulation of physiologic functions such as

1. Gastric protection
2. Vascular homostasis & platelet aggregation
3. Kidney function

Cox-2

only in certain conditions it gets expressed.

- Cox-2 is an inducible enzyme produced by inflammatory cells
- It catalyzes production of pro-inflammatory PGs as mediators for inflammation
- It is constitutively expressed in brain (fever induction and pain transmission), kidney (water & electrolyte homeostasis) and bone.
- It's expression is elevated at other sites during state of inflammation

Mechanism of action

- NSAIDs act by inhibiting cyclooxygenase enzymes that catalyze first step in prostanoids biosynthesis, leading to decreased PGs synthesis with both beneficial & unwanted effects

- Most NSAIDS are non-selective i.e. they inhibit both Cox-1 and Cox-2 . Their anti-inflammatory action is due to inhibition of Cox-2, but side effects are due to inhibition of Cox-1

→ Not specific for a specific enzyme x!

@ Non selective Cox Inhibitors may disrupt the balance of Cox-1 and Cox-2. So you need to be careful when prescribing 'em

@ Main ADR's for the NSAID is the GI problems!

Gx→ Maybe caused by taking 'em for long periods

Therapeutic uses

1. Anti-inflammatory effect:

- To treat inflammatory disorders e.g. Rheumatoid arthritis (RA), osteoarthritis (OA), gout, and musculoskeletal disorders

NSAIDs decrease inflammation by decreasing PG production, but inflammation is not abolished because of presence of other inflammatory mediators

- NSAIDs give some relief of pain, swelling, and stiffness.

2. Analgesia:

Voltarin ⇒ Most powerful Analgesic from the NSAID's

- NSAIDs relieve mild to moderate pain e.g headache, dental pain, muscle or joint pain and soft tissue pain.

- NSAIDs are not effective for severe pain

So the other option is the opioids!

NSAIDs decrease pain by decreasing production of PGs responsible for sensitization of nerve endings to action chemical mediators (bradykinin & histamine) in inflamed tissue

3. Antipyretic effect:

- NSAIDs decrease pyrexia due to inflammation, trauma, allergy but has no effect on the normal body temperature
- Fever occurs when Macrophages, at site of inflammation, produce interleukin-1 (IL-1) which enters CNS to act on hypothalamus to stimulate PGE_2 synthesis; this PGE sets the hypothalamus thermostat at a higher level and thus produces pyrexia

NSAIDs decrease pyrexia by inhibiting the PGs synthesis in hypothalamus, therefore setting thermostat at lower level

4. Anti-platelet effect:

- **Aspirin** is indicated to reduce the incidence of myocardial infarction (MI), transient ischemic attacks (TIA) & embolic strokes that all caused by vascular thrombosis due to platelet aggregation.
- Aspirin at low dose (80-100 mg/d) **irreversibly inhibits the thromboxane A_2** (TXA_2) synthesis inside platelets **via acetylation of Cox-1.** (TXA_2 is a powerful platelet aggregator and a vasoconstrictor)

- The decrease in TXA_2 leads to inhibition of platelets aggregation , and prevents thrombosis in arteries of brain (cerebral), heart (coronary), and limbs.

Adverse effects

1. **GIT:**

- PGs have gastroprotective effect: inhibiting acid secretion, promoting secretion of mucous

So we give another drugs to reduce the ADR's, ex => Proton Pump Inhibitors.

- NSAIDs decrease formation of protective PGs in gastrointestinal mucosa and therefore leading to GI irritation, GI bleeding and ulcers

- These side effects can be treated by coadministration of Proton-pump inhibitors (PPIs), H-2 antihistamines & prostaglandin analogue (misoprostol)

? why misused for child Abortion!

2. Renal effects:

- NSAIDs decrease renal blood flow due to inhibition of synthesis of renal PGs eg. PGI2
- This results in retention of sodium and water and may cause edema. This makes heart failure or hypertension more worse.
- Chronic use (= long term use) of NSAIDs (esp. multiple of them) may lead to interstitial nephritis progressing to renal failure

3. Bleeding :

- Because of platelet dysfunction especially with aspirin, bleeding time is prolonged.
- Carful should be taken before surgery and in patients administering anti-coagulant

Protocol ⇒ Stop NSAID's before 2 weeks of Surgery!

4. Pregnancy :

- NSAIDs should be avoided because they can cause :
  a. delayed onset of labor , and prolonged labor
  b. premature closure of the ductus arteriosus in infant
  c. increased risk of bleeding during labour.

5. CNS :

- Headache, vertigo, dizziness, confusion & depression
  ex ⇒ Endomathezin

6. **Hypersensitivity**:

- Vasomotor rhinitis, edema, asthma, urticaria flushing, hypotension and shock.

7. **Liver toxicity :**

- With large doses esp. with prolonged use or in patients with liver disease, all NSAID's are metabolized in the liver.

8. **Skin effects :**

- **Specially with topical use:** photosensitivity, allergy e.g. urticaria, & other skin rashes.

Drug interactions

1. Many **NSAIDs are highly bound to plasma albumin** after their absorption from GIT. Accordingly, they may displace other drugs that are also bound to plasma albumin (e.g. warfarin , hypoglycemic sulphonylureas drugs) to become free and active in plasma which may result in toxic effects of these drugs

2. NSAIDs , mainly due their renal actions , may **antagonize the effect of diuretics as well as anti-hypertensive drugs** like beta-adrenoceptor → Ex → Propranolol, Metoprolol... blockers & ACE (Angiotensin-Converting Enzyme) inhibitors

Contraindications

- NSAIDs use should be avoided:

  Peptic ulcer

  Renal impairment

  Cardiac failure

  Bleeding disorder

  Pregnancy

- Caution is needed in patients with bronchial asthma or hypertension

- NSAIDs should be avoided or used with caution in liver disease as all NSAIDs are metabolized by liver

because you don't want to worsen the diseases!

lec 2

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Classification of NSAIDs

- Based on their anti-inflammatory action:

A. Weak or No clinically useful anti – inflammatory action eg. Paracetamol

B. Mild to moderate anti-inflammatory action eg. Aspririn

C. Marked Anti-inflammatory action eg.

Diclofenac ⇒ Voltarin

End of Lecture 1

A. Weak or No clinically useful anti – inflammatory action

1. **Paracetamol or Acetaminophen (Panadol):**

- Paracetamol has an analgesic and antipyretic properties with a devoid of anti-inflammatory effect.
- It inhibits PGs in brain and therefore acts as analgesic and antipyretic but it has less effect on peripheral PGs responsible for inflammation.

It probably act on another enzyme, (COX_3), in CNS, which may be a splice variant product of COX_1 gene, to produce analgesic or antipyretic effects.

- It is a weak inhibitor of COX1 or COX2

In periphery , it has no significant anti-inflammatory action .
In tissues , p-aminophenols trap free radicals which are important for formation of hydro-peroxidase that is essential for the activity of COX .

In inflamed tissues, large amounts of peroxide radicals are produced which swamp this action of p-aminophenols ; thus hydroperoxidase continue to be formed, and COX_2 remain active in inflammatory cells at inflamed sites

Para

- It neither affects platelet function nor GI irritation
- The oral dose for adults as analgesic or antipyretic is 0.5 -1 g X 3/d. 0.5 ⇒ Per pill
- Maximum daily dose is 4 g

➢ Therapeutic uses:

1. It is effective in mild to moderate pain e.g. headache, dysmenorrhoea (menstrual pain)
2. It is a substitute for analgesic & antipyretic effects of aspirin particularly in

   A. children with viral infection !!

   B. patients with peptic ulcer since it causes no gastric irritation

➢ Adverse effects include:

1. Skin rash occurs infrequently
2. Hepatic and renal necrosis with large and prolonged doses (quinone metabolite). Antidote is N- acetyl cysteine binds and inactivates the toxic quinone metabolite

B. Mild to moderate anti-inflammatory action

1. Aspirin (Acetylsalicylic acid)

- It is a weak organic acid and is unique among NSAIDs.
- Mechanism of action:

Aspirin Irreversibly inhibits Cox by acylating active site of enzyme, so preventing formation of thromboxane, prostacyline & other PGs.

- Other NSAIDs are reversible inhibitors of Cox

Aspirin لـ هو اهم مختلف فقط ⊗

➢ Therapeutic uses:

1. Anti-inflammatory use :

- RA, OA and other inflammatory joint disease.
- Dose is 4-6 g / d in 3-4 divided doses

2. Analgesic and anti-pyretic use:

- Fever, headache, toothache, and muscular and joint pain
- Dose is 325-650 mg X 3 / d

3. Anti-platelet use :

Remember the protocol of Surgery

- Low dose of aspirin 80-100 mg daily are used to prophylactically decrease incidence of transient ischemic attacks (TIAs) & strokes , Prevent Thrombosis .

Adverse effects:

1. GIT:

- Epigastric distress, nausea, vomiting and bleeding

2. Bleeding tendency

3. Hypersensitivity:

- About 15% of patients develop allergy

4. Specific adverse effects :

A. Reye's syndrome:

- Use of Aspirin in children with viral infections (e.g. measles, influenza, or chickenpox) may rarely cause Reye's syndrome (extensive fatty infiltration of liver with liver damage and failure)

B. Salicylism :

- It is mild salicylic acid intoxication. Symptoms include: confusion, tinnitus, deafness, sweating, vomiting and others , more common ⇒ in 325mg.

- **Contraindications:**

- Aspirin should be avoided in patients with peptic ulcers, asthma and febrile children due to viral infections.

- **Drug interactions:**

- Aspirin should be avoided or used with caution in patients taking warfarin, phenytoin or valporic acid. Aspirin displaces these drugs from binding of plasma protein resulting in high drug concentrations and therefore toxicity

2. Propioinc acid derivatives

(ketacin) (golfact)

- This class includes Ibuprofen , ketoprofen and Naproxen → No pain, used by dentists.
- All are reversible non-selective inhibitors of Cox that inhibit synthesis of PGs
- All possess anti-inflammatory, analgesic & antipyretic activities
- They cause less GI side effects than aspirin and therefore are preferred for chronic use in inflammatory joint diseases and in musculo-skeletal disorders
- Most common adverse effects ranges from GI dyspepsia to bleeding → after years of taking it.

3.Fenamates :

- Main example is Mefenamic acid (ponstan)
- No clear advantages over other NSAIDs and may cause GI side effects. It has little anti-inflammatory action (milde).
- Indications:
- Short-term treatment of pain in soft-tissue injuries, dysmenorrhea, and in RA and OA
- Adverse effects:
- Severe diarrhea associated with inflammation in bowel and hemolytic anemia

why? 3-4 days

caused

C. Marked Anti-inflammatory action

1. Arylacetic acid derivatives :

- Main example is Diclofenac (Voltaren)
- It is a potent Cox inhibitor with anti-inflammatory, analgesic & antipyretic activities (accumulates in synovial fluid)
- It is potent than indomethacin or naproxen
- Indications:
- long-term treatment of RA and OA
- short-term treatment of acute musculoskeletal pain, postoperative pain, and dysmenorrhea
- Side effects:

a. GI irritation to bleeding
b. Fluid retention, edema, and rarely impairment of renal function ⇒ Particulary (gdfast)

2. Acetic acid derivatives: ⇒Most used for(arthritis). very Powerful, but has many side-effects

- Indomethacin (Indocin) and sulindac
- All possess anti-inflammatory, analgesic and antipyretic properties
- They are not generally used to lower fever

A. Indomethacin :

- It is more potent than aspirin, but toxicity limits its use to short-term dosing
- Indications:
- It is useful in treatment of RA,OA, ankylosing spondylitis (AS), and acute gout

2. Closure of patent ductus arteriosus in neonate : given by IV infusion within 72 h of birth (Indicated) But!! ⇒ before birth is not indicated.

- Side effects :
- CNS : (35-50%)headache, dizziness and others
- GI disturbances: Diarrhea, ulcers, bleeding

B. Sulindac :

- This is a pro-drug ; it is converted to active sulfide metabolite in liver
- It is less potent than indomethacin
- It causes less adverse effects than indomethacin & other NSAIDs
- It is useful in treatment of RA,OA, AS and acute gout

3. Oxicam derivatives :

used for treatment of joint pain.

- Piroxicam (Feldene) and meloxicam (Mobic)
- Able to inhibit Cox-1 and Cox-2 but meloxicam shows preferential COX-2 selectivity (preferential Cox-2 inhibitor)

↳ Some selectivity → 30% - 70%

- Are used to treat RA, OA, AS
- They have long half-life, once daily
- Piroxicam has more GI side-effects than most other NSAIDs
- Meloxicam has significantly less GI side-effects compared to piroxicam and other NSAIDs

COX-1 ⇒ causing ADR's
COX-2 ⇒ causing Inflammation.

4. Selective Cox-2 inhibtors (coxibs)

- Celecoxib, rofecoxib, valdecoxib and etoricoxib
- Analgesic and anti-inflammatory properties by selectively inhibiting the Cox-2 biosynthesis
- **Hypothesis**: Cox-2 isoform is up regulated in the site of inflammation mediating inflammation by catalyzing the biosynthesis of PGE2 and PGI2 , and these PGs are also formed by Cox-1 in gastric epithelium where they act as cytoprotective mediators.

- proinflammatory PGs are inhibited and simultaneously sparing the PGs catalyzed by Cox-1 necessary for physiologic functions
- They exert anti-inflammatory properties with less or none of typical adverse effects associated with NSAIDs treatment on GIT and kidney.
- **Indications:**
- Patients who require chronic use of NSAIDs & are at high risk for NSAIDs-induced ulcer

- Inflammatory and painful conditions such as RA, OA, headache, menstrual, dental and postoperative pain
- Long acting, once daily
- **Side effects:**
- Most common abdominal pain, diarrhea, dyspepsia
- Hypersensitivity:sulphonamide hypersensitive patients (urticaria, angioedema, sweet, rash... Etc)

➢ Contraindications:

- ➢ COX-2 inhibitors should be avoided in patients with chronic renal insufficiency, severe heart disease & hepatic failure.

- ➢ Rofecoxib and valdecoxib was withdrawn from market because its use was associated with increased risk of stroke, heart attack, and sudden cardiac death.

duration ⇒ 17 hrs.

13 hrs.

because it disrubted the balance betweeen COX-1 and COX-2 !!!
COX-1 is essential for the synthesis of TxA2, which stimulates platelet aggregation and vasoconstriction, and thus exerts hemostatic/ thrombogenic effect.