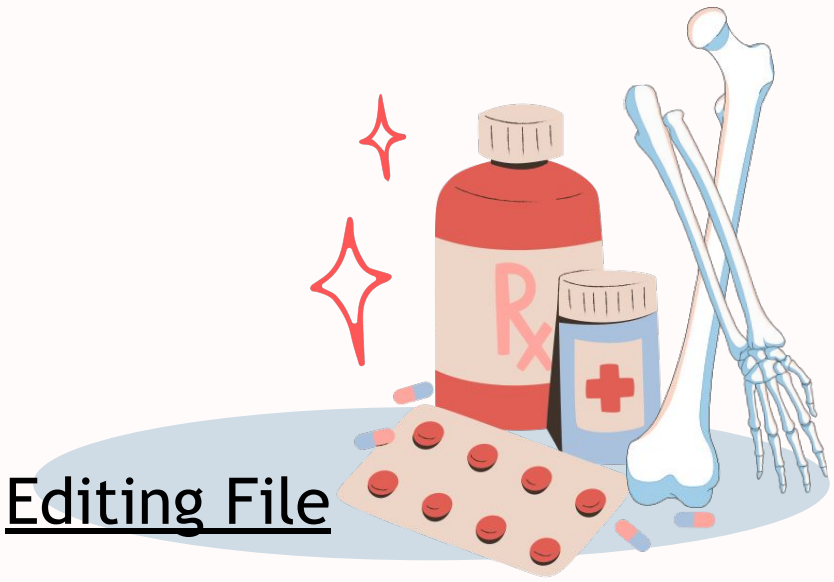
NSAIDs

Lecture no.4

Color Index:

- Main Text
- Important
- Females' Slides
- Males' Slides
- Drs' Notes
- Extra info.



Editing File

(اللَّهُمَّ انفَعْنِي بِمَا عَلَّمْتَنِي، وَعَلِّمْنِي مَا يَنْفَعُنِي وَزِدْنِي عِلمًا)

Objectives

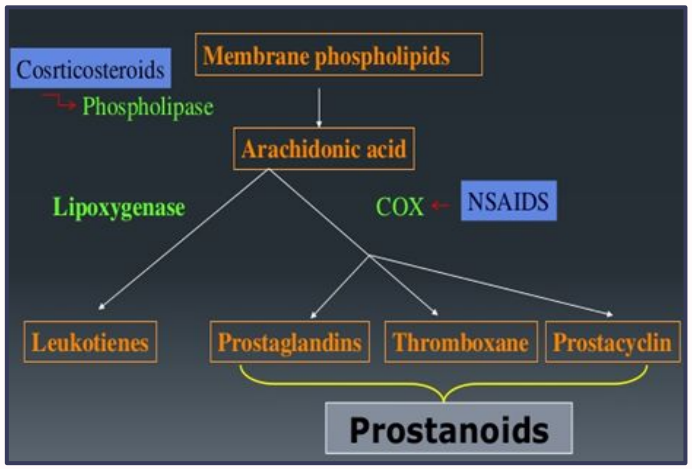
- To focus on the general mechanism of action of NSAIDs.
- To classify NSAIDs on basis of their specificity to COX isoenzymes.
- To outline the common pharmacodynamic effect and ADRs of NSAIDs.
- To detail on the pharmacokinetic properties and pharmacodynamic effects of selected NSAIDs.

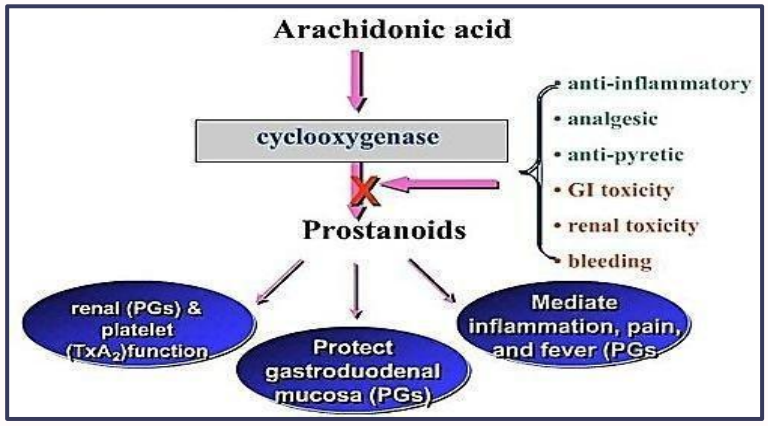
NSAIDs EPIDEMIOLOGY

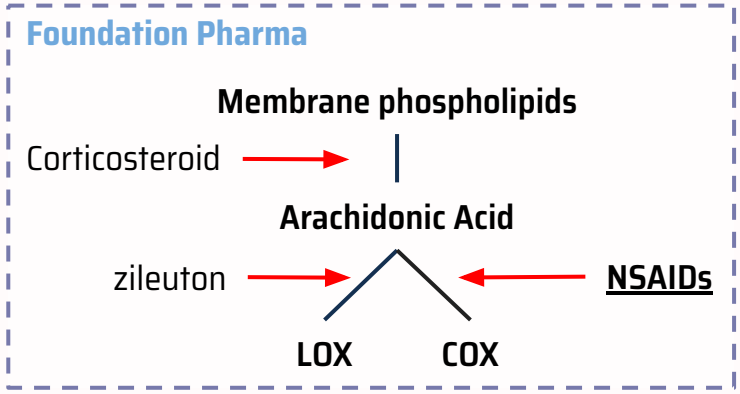
1- NSAIDs account for 3.8% of all prescriptions.
2- A significant quantity is sold over the counter (OTC). OTC means that can be sold without prescription.
3- Use increases with age.
4- 90% of all NSAIDs prescriptions are issued to patients at ages over 65 years.
5- NSAIDs is the most prominent risk for gastric ulceration, hemorrhage and perforation.
6- The prevalence of NSAIDs-induced ulcers is 10% -30%

NSAIDs M.O.A

NSAIDs inhibit cyclooxygenase enzyme (COX) which leads to the inhibition of prostanoids synthesis.There is another pathway that NSAIDs won't act on (Lipoxygenase).







COX Isoforms

COX-1 “constitutive”

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

Inhibiting COX-1 with NSAIDs may cause ulcers in the stomach and promote bleeding. “Undesirable effect”

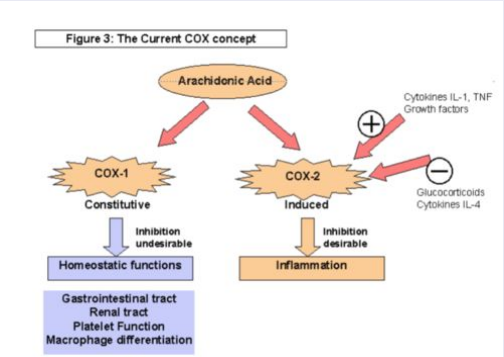
COX-2 “Induced”

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

Inhibiting COX-2 with NSAIDs will reduce pain and inflammation “desirable effect”.

COX-3

In the brain, so drugs targeting COX-3 are safe for use during pregnancy



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).

Pharma 438:
NSAIDs: Non steroidal anti inflammatory drugs, are group of drugs that share in common the capacity to induce the following effects in the next page.

NSAIDs Effects

Analgesic مُسكن

Inflammatory factors increase PGs, Bradykinin and Histamine. Those three would stimulate nociceptors at nerve endings which can cause pain. Another job for PGs is to increase Bradykinin and histamine, so NSAIDs Analgesic would decrease PGs ---> decreasing Bradykinin and histamine

-Mechanism: Block PGs production.

-Site of Action: peripheral tissue.

-Used for:
Headache, Migraine, Dental pain, Dysmenorrhea (painful menstruation and abdominal cramps).

Antipyretic
خافض للحرارة

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 (↑ metabolism) and ↓ heat dissipation (loss) (↓metabolism, ↑sweat), resulting in FEVER.

- Mechanism: Block PGs production.

-Site of action:CNS.

-Used for:
reducing fever back to normal body temperature.

Anti-Inflammatory

The (5-Ht) Histamine, bradykinin, and inflammatory factors will stimulate the PG which will cause symptoms of inflammation: pain, redness, heat, swelling.

Mechanism:
Block PGs production.

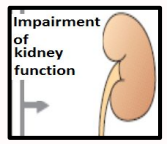
Site of Action: peripheral tissue.

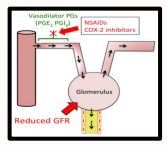
Used for:
Rheumatoid arthritis/ Myositis, inflammation and degeneration of muscle tissue, Common cold.

it’s animated in the slides but here’s the explanation

ADRS of NSAIDs

1- GIT upset: (nausea, vomiting).
2- GIT bleeding and ulceration.(due to to blockage of constitutive COX which protects GIT).
3- Hypersensitivity reaction.
4- Inhibition of uterine contraction.
(By blockage of constitutive COX and reducing PGs which induce labor by contraction).
5- Salt and water retention.Decreased excretion due to reduced GFR.
6- NSAIDs cause hemodynamically-mediated acute failure.(COX1 would produce PGF2 and PGI2 that are vasodilators for renal tubules, preventing them would inhibit vasodilation ---> decreasing GFR causing renal failure.).Can be detected by (Cystatin C) (Foundation boimarkers)





In more detail : (HUGE THANKS TO TEAM 435)
Prostaglandins (PGE2 & PGI2) cause vasodilation of the afferent arterioles of the glomeruli.
This helps maintain normal renal blood flow and GFR. NSAIDs prevent the synthesis of PGE2 & PGI2 by Inhibition of both COX-1 & COX-2 enzymes (mainly COX-2). Decreased synthesis of PGs results in retention of sodium and water, causing edema of lower limbs in some patients, hyperkalemia & interstitial nephritis.Patients with a history of heart failure or kidney disease are at particularly high risk.

Clinical Uses of NSAIDs

1. FEVER
2. Headache, Migraine,Dental pain Dysmenorrhea.
3. Common Cold
4. Rheumatoid arthritis / myositis

Classification of NSAIDs

Nonselective COX1/COX2 Inhibitors	Aspirin, Diclofenac, piroxicam, Ibuprofen, naproxen, ketoprofen,indomethacin
Selective COX-2 Inhibitors	Coxibs (Celecoxib, Etoricoxib, Parecoxib, Lumiracoxib)
Preferential COX-2 Inhibitors	Meloxicam, Nimesulide, Nabumetone.
COX-3 Inhibitors	Paracetamol (is not NSAID)

Non selective Cox 1,2 Inhibitors

Aspirin, Diclofenac (voltaren), Piroxicam, Ibuprofen, Naproxen,Ketoprofen,Indomethacin

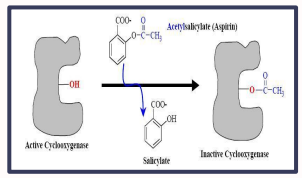
1.Aspirin (Acetylsalicylate)

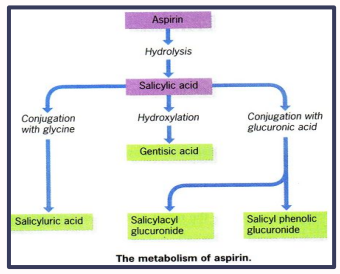
M.O.A

Aspirin binds with the active site of COX enzyme and makes it inactive. Aspirin inhibits COX **irreversibly**.
(All NSAIDs bind **reversibly** except Aspirin).

P.K

Metabolized by hydrolysis to **Salicylic Acid** then conjugation:
1- Conjugation with glycine
2- Conjugation with glucuronic acid
3- Hydroxylation



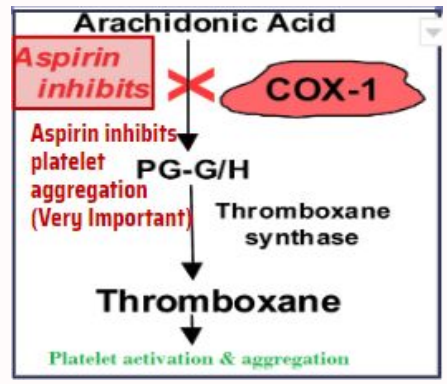


Why does a high dose of Aspirin have a long plasma half-life?
Pharma 439: Aspirin follows 1) Zero-Order kinetics, meaning that the rate of elimination is constant regardless of the concentration. 2) saturation of metabolize enzyme.

Clinical uses

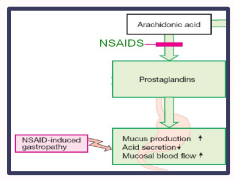
- Acute rheumatic fever.
- Reduces the risk of myocardial infarction (cardioprotective).
- Inhibition of thrombosis formation. Most important effect.
They prevent platelet COX 1, inhibiting TXA2 formation which is essential for platelet aggregation. (As seen in the picture)
- Prevention of pre-eclampsia تسمم الحمل (increase in BP during pregnancy)
- Chronic use of small doses reduce the incidence of colon cancer.
(Doctor says we still don't know really why).

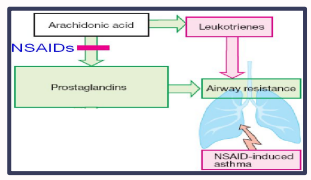
443 note : Aspirin is not recommended for:
1-tremors 2-bleeding 3-deformities in fetus (pregnancy) 4-delayed delivery



ADRs at clinical dose

1-Hypersensitivity
2-Acute gouty arthritis due to uric acid retention (Low doses -> prevent uric acid excretion -> leads to accumulation -> Gout)
3-Reye's syndrome Affects children with viral infection who take aspirin. (Reye's syndrome is rare but is a serious encephalopathy & causes fatty degenerative liver failure (swelling in the liver and brain).
4-Impaired haemostasis. Inhibit platelet aggregation -> prevent clotting -> cause bleeding
5-GIT side effects, dyspepsia, nausea and vomiting
6-Mucosal damage → hemorrhage
7-Bronchospasm in aspirin- sensitive asthmatics (Cuz LOX is still working).



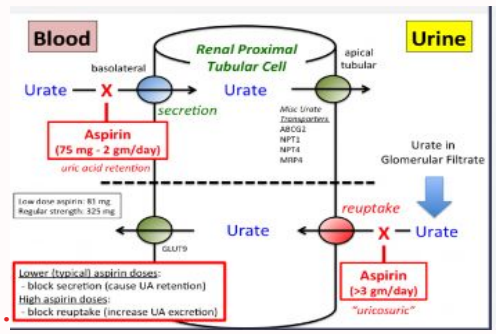


ADRs at overdose

Salicylism (ringing of ear, vertigo), Hyperthermia, Gastric ulceration and bleeding.

Contraindications

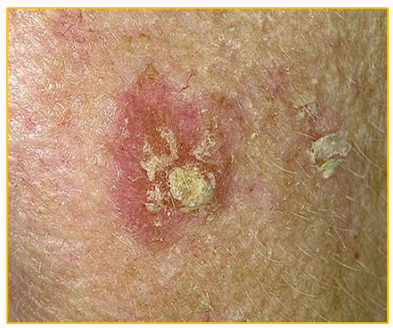
1-Peptic ulcer
2-Pregnancy (paracetamol is the safest during pregnancy).
3-Hemophilic Patients
4-Patients taking anticoagulant, it may cause excessive bleeding.
5-Children with viral infections (Cuz it might develop Reye's syndrome)
6-Gout (at small dose):
★ Small dose of aspirin cause retention of uric acid cuz of blockage of secretion.
While the high dose causes an Increase in uric acid excretion By blockage of reabsorption.



Non Selective Cox 1,2 Inhibitors

2. DICLOFENAC

Clinical uses	1- Analgesic. 2- Antipyretic. 3- Anti-inflammatory. 4- Acute gouty arthritis. 5- 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.)
Preparations	1- Diclofenac with misoprostol (Prostaglandin analog) 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 for pain & fever 7- Rectal suppository as analgesic.



Selective cox-2 Inhibitors

Coxibs: (Celecoxib, Etoricoxib, Parecoxib, Lumiracoxib).

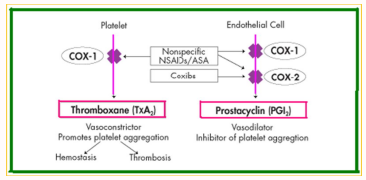
Coxibs

M.O.A

- Potent anti-inflammatory.
- Antipyretic & analgesic.
- Lower incidence of gastric upset.
- No effect on **platelet aggregation** (COX-1) and stomach (safe for patients with peptic ulcer).

General ADRs

- Allergy.
- Dyspepsia & heartburn.
- Renal toxicity.
- **Cardiovascular** (Do not offer the cardioprotective effects of non-selective group).
- should not be given to a patient with CV disease.(cox2 creates PGI2 and cox1->TXA2)



Clinical uses

- Short-term use in postoperative patients.
- Acute gouty arthritis.
- Acute musculoskeletal pain.
- Ankylosing spondylitis (spine arthritis).

P.k

- t1/2= 11 hours.
- Food decreases its absorption (shouldn't be given with food)
- Highly bound to plasma proteins.
- Contraindicated in patients allergic to sulfonamides.

Preferential COX-2 Inhibitors:

Meloxicam, Nimesulide, Nabumetone.

Notes

- Preferentially inhibit COX-2 over COX-1 particularly at low doses. (They are non-selective but inhibit COX-2 more at low doses).
- t1/2=20 hours
- Associated with lower GIT symptoms & complains, compared to non-selective COX inhibitors.
- Used for Osteoarthritis and rheumatoid arthritis.

- It becomes non selective in the case of an overdose.

COX-3 Inhibitors:

Paracetamol (Acetaminophen).

P.k

- Given orally ,well absorbed
- Metabolized by conjugation at therapeutic doses
- t1/2 =2-4 h

Action

- Antipyretic, Analgesic
- Weak anti-inflammatory effect (Not used as anti inflammatory)
- Binding of paracetamol to COX is inhibited by peroxides produced in inflammatory sites.
- There is no evidence that COX 3 exists in humans.

Clinical Uses

Commonly used as an analgesic and antipyretic instead of aspirin in cases of:

- Peptic or gastric ulcers.
- Pregnancy.
- Viral infections in children.
- Bleeding tendency (No cardio protection since it doesn't affect COX-1).
- Allergy to aspirin.

ADRs

Mainly on liver due to its active metabolite:

- Therapeutic doses elevate liver enzymes (no significant ADR).
- Large doses metabolized into N- acetyl-p-benzoquinone imine, which causes liver damage.
- Chronic abuse lead to Nephrotoxicity.

★ Treatment of toxicity of paracetamol is by N- acetylcysteine to neutralize the toxic metabolite.

MCQs

Q1. Among NSAIDs, aspirin is unique because it:			
a) Irreversibly inhibits target enzyme.	b) Reduces fever.	c) Selectively inhibits the COX-2 enzyme.	d) Increases the risk of colon cancer.

Q2. Meloxicam is an example of which of the following?			
a) Preferential COX-2 inhibitor	b) selective COX-1 inhibitor.	c) COX-3 inhibitor	d) Selective COX-2 inhibitor

Q3. Which of the following drugs should not be prescribed to children with Reye's Syndrome?			
a) Celecoxib	b)Aspirin	c) Paracetamol	d) Ketoprofen

Q4. Which of the following is safe for use by pregnant women?			
a) Paracetamol	b) Aspirin	c) Diclofenac	d) ARB

Q5. One of the contraindications of Celecoxib is?			
a) rheumatoid arthritis	b) osteoarthritis	c) Sulfonamides allergy	d) peptic ulcer

Answers:
1)A
2)A
3)B
4)A
5)C

SAQs

1 **Mention THREE general adverse effects for NSAIDs?**

- Hypersensitivity reaction
- GI bleeding & ulceration
- Nausea & vomiting

2 **Describe the mechanism of action of NSAIDs:**

They inhibit cycloOxygenase enzyme (COX) which leads to inhibition of prostanoids synthesis

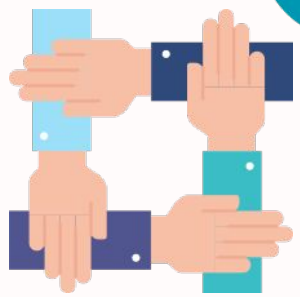
3 **Name ONE contraindication for the use of celecoxib?**

patient with CV diseases.

4 **What is the antidote of paracetamol toxicity?**

N- acetylcysteine.

Team Leaders:



- Rakan Almutib
- Shoug Albattah

Team Members:

- Khalid Alkanhal
- Omar Alattas
- Waleed Alanazi
- Ali Al-Abdulazem
- Saleh Alotaibi
- Fawaz Almadi
- Jenan Alsayari
- Lama Alahmari
- Wsaif Alotaibi
- Nora Alturki
- Sahar Alfallaj
- Madaen Alarifi

Contact us at : pharmacology.444ksu@gmail.com