Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY

Non-steroidal Anti-inflammatory Drugs

"NSAIDs"

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 specifity to COX enzyme
- ✓ To detail on the pharmacokinetic properties and pharmacodynamic effects of selected NSAIDs

Editing File

Important Notes Extra

Overview Of NSAIDs

What are NSAIDs?

A drug class that provide analgesic (pain killer) and antipyretic effect (lower temperature) and have anti- inflammatory effects. In addition, it's called (non- steroid) to distinguish from steroid drugs.

❖ Mechanism of action:

Inhibition of Cyclo Oxygenase (COX) enzyme which lead to the inhibition of Prostaglandin synthesis. All actions and side effects are due to this inhibition.

❖ COX Isoforms :

COX-1:	COX-2:	COX-3:
Hemostatic functions	Inflammation inducer	Found in the brain.
Its inhibition is not desirable due to its ADRS	Its inhibition is desirable.	

❖ Pharmacodynamic effects (action of) NSAIDs:

1- Analgesic :

NSAIDs inhibit the formation of PGE2 & PGF2 causing analgesia (pain killer) in peripheral tissue. Prostaglandin stimulates the pain receptors (Nociceptors) so inhibiting its synthesis will relieve pain. (More details about pain will be discussed in CNS block).

2- Antipyretic :

NSAIDs inhibit the formation of PGE2 which activates the thermoregulatory center to raise Heat production and inhibit dissipation (Fever) in CNS. Act on relieving moderate fever not a severe one. It decreases heat by causing vasodilatation and sweating.

3-Anti-inflammatory:

NSAIDs inhibit the formation of PGE2 & PGF2 which cause Redness, swelling, Heat and Pain in association with Bradykinin, Histamine and 5-HT. site of action : peripheral tissue. All have this effect except Paracetamol.

Clinical uses of Analgesic, Antipyretic, and Anti-inflammatory :

- ❖ Fever
- ❖ Headache, Migraine (only in mild to moderate migraine)
- ❖ Dental pain, Dysmenorrhea (painful period)
- ❖ Common cold
- ❖ Rheumatoid arthritis / myositis

✓ NSAIDs are given to relieve mild to moderate pain not severe one!

General ADRS: GIT side effects are VERY important!

- ❖ NSAIDs cause hemodynamically- mediated acute renal failure. With large doses.
- ❖ **GIT upsets (nausea, vomiting)**
- ❖ **GIT bleeding & ulceration** with prolong use and overdose may lead to perforating peptic ulcer
- ❖ Hypersensitivity reactions (Because of Leukotrienes which their enzyme –Lipoxygenase- is not inhibited)
- ❖ Inhibition of uterine contraction it can be used during labor
- ❖ Salt & water retention

Classification of NSAIDs

TYPE	EXAMPLE
Nonselective (inhibit COX1&2)	**Aspirin and Diclofenac**
Selective COX-2 (inhibit only COX-2)	**Coxibs**
Preferential COX-2 inhibitors	**Meloxicam**
COX-3 inhibitors	**Paracetamol**

✓ Note that nonselective must be taken after eating while selective COX-2 can be taken on an empty stomach.

Non selective COX inhibitors:

This class inhibits both COX-1 and COX-2 but its effect is more potent on COX-1 (many ADRS). Those drugs include:

Aspirin Diclofenac	Ibuprofen Ketoprofen	Naproxen Piroxicam Indomethacin

Note that Ibuprofen is a potent anti-inflammatory drug. Indomethacin is not used anymore due its severe ADRS.

Drug	**Aspirin (Acetylsalicylate)**	
MOA	Inhibits COX (non selective) irreversibly by acetylation.	
P.K	1. Higher dose of aspirin has a long plasma half- life. 2. Metabolized by hydrolysis and then conjugation. 3. Zero order kinetic elimination. The rate of elimination is constant even if you increased the dose causing accumulation. Due to plasma protein binding- zero order of kinetics – wild volume of distribution	
Clinical Uses	1. Acute rheumatic fever. 2. Reducing the risk of myocardial infarction (cardioprotective). Inhibition of thrombosis formation. Small doses are used as prophylactic therapy. 3. Prevention of pre-eclampsia.تسمم الحمل 4. Chronic use of small doses reduce the incidence of colon cancer. The reason is unknown.	
ADRs	**Clinical dose:** • Hypersensitivity **bronchospasm**, rhinitis, conjunctivitis, urticaria • Acute gouty arthritis (low doses) • Reye's syndrome. Affects children with viral infection who takes aspirin. • Impaired hemostasis. Bleeding • GIT side effects, dyspepsia, nausea and vomiting • Mucosal damage → hemorrhage	**Overdose:** • **Salicylism (ringing of ear, vertigo)** • **Hyperthermia** while therapeutic dose decreases the fever • Gastric ulceration & bleeding

Aspirin cont..

Contraindication

1. Peptic ulcer.
2. Patients taking Anticoagulants.
3. Hemophilic patients.
4. Children with viral infections. (Reye's Syndrome)
5. Pregnancy.
6. Gout (small doses).
7. **Asthmatic patients**. Aspirin induced asthma

Drug interaction

Taking Aspirin with antacid should be avoided because it reduces the absorption of aspirin by reducing the acidity media which is required for aspirin absorption.

Aspirin dose:

Low dose:

uric acid retention, prevent urate secretion to proximal tubular cell, hence, High in blood, low in urine.

Cause GOUT

Large dose:

Prevent Urate from reabsorption hence high in urine, low in blood

Uricosuria

Treat GOUT

Drug

Diclofenac

Clinical uses

1. Analgesic.
2. Antipyretic.
3. Anti-inflammatory. Strong effect
4. Acute gouty arthritis.
5. Locally to prevent post-operative ophthalmic inflammation.

Preparations

- **Diclofenac (could be given) with misoprostol (type of PGE1) decreases upper gastrointestinal ulceration , but result in diarrhea.**
- **Diclofenac with omeprazole (decrease acidity) to prevent recurrent bleeding.**
- 0.1% ophthalmic preparation for postoperative ophthalmic inflammation.
- A topical gel 3% for solar keratoses.
- Rectal suppository as analgesic . Given to children with fever
- Oral mouth wash.
- Intramuscular preparations.

Selective COX-2 inhibitors:

This group of drugs of NSAIDs inhibit COX-2 selectively with no effect on COX-1. Those drugs include:

Celecoxib
Etoricoxib

Paracoxib
Lumiracoxib

Rofecoxib
*Valdecoxib

Valdecoxib is converted into Rofecoxib

*It is withdrawn because of risk of myocardial infarction and stroke

General Action	• **Potent anti-inflammatory.** • **Antipyretic & analgesic.** • **Lower incidence of gastric upset.** • **No effect on platelet aggregation(COX-1)** **No cardioprotective effect**
General ADRs	• Renal toxicity • Cardio vascular do not offer the cardio-protective effects of non-selective group (not anti-platelet) COX-2 is found only in endothelial cells where Prostacyclin is found and Thromboxane is NOT found. • Dyspepsia & Allergy heartburn it is not as potent as the one caused by COX-1 inhibitors • Allergy
Clinical Uses	1. Short-term use in post operative patients to reduce inflammation and increased body temperature 2. Acute gouty arthritis **3. Acute musculoskeletal pain** (cause it's potent anti-inflammatory). **4. Ankylosing spondylitis** (inflammation in the joints of spine, leading to pain and stiffness) (muscle pain)
Contra diction	❖ Shouldn't be given to a patient with CV diseases.

Drug	Celecoxib	Meloxicam, Nimesulide, Nambumetone
P.K	• Half-life 11 hours • Food decreases its absorption (Not given with food) • Highly bounded to plasma proteins	Half-life 20 hours prolong effect
MOA	Selective COX-2 inhibitor It is the best among those inhibitors	• **Preferentially inhibits COX-2 over COX-1, particularly at low dose** • The most important one is Meloxicam
Indication	-	**Used for Osteoarthritis and rheumatoid arthritis**
ADRs	-	Associated with lower GIT symptoms and complains compared to non-selective COX inhibitors
Contradiction	**Contraindicated in patients with Sulphonamides allergy.**	-

Selective COX-3 inhibitors:

Drug	Paracetamol (Acetaminophen)
MOA	Selectively inhibits the COX-3. Found in the brain. **Weak anti-inflammatory effect**. It is not given in conditions associated with inflammation
P.K	Given orally , well absorbed. t½=2-4 h. Metabolized by conjugation at therapeutic doses. Binding of paracetamol to COX is inhibited by peroxides produce in inflammatory sites. There is no evidence that COX3 exists in humans.
Indications	Commonly used **analgesic antipyretic** instead of Aspirin in cases of: • Peptic or gastric ulcers • Bleeding tendency • Allergy to Aspirin • Viral infections in children • Pregnancy
ADRs	Mainly on the liver due to its active metabolite (N- acetyl-p-benzoquinone imine) with large doses which causes liver damage (Hepatotoxicity). Therapeutic doses causes only liver enzymes elevation. No significant ADRS. Chronic abuse causes Nephrotoxicity.
Toxicity	**The toxicity caused by large doses of Paracetamol is treated by N-acetylcysteine to neutralize the toxic metabolite. VERY IMPORTANT!** Note: Any drug used to overcome a toxicity we call it Antidot.

Paracetamol VS Aspirin:

Clinical uses of Paracetamol	Contraindications of Aspirin
Peptic or gastric ulcers	Peptic ulcer
Bleeding tendency	Hemophilic Patients, Patients taking Anticoagulants.
Viral infections in children	Children with viral infections
Pregnancy	Pregnancy
Allergy to aspirin	Gout (small doses)

Summary

*This summary is from Lippincott

Helpful videos:

https://www.youtube.com/watch?v=LQpQtBEGkU4&index=33&list=WL

https://www.youtube.com/watch?v=VXR0Xiif25M&list=WL&index=34 (turn off the volume)

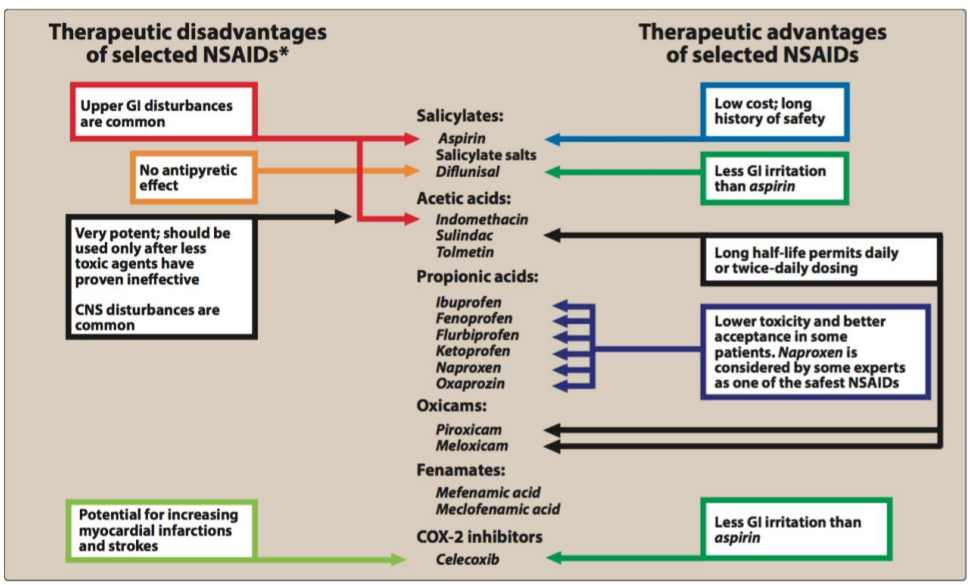


Figure 36.15
Summary of nonsteroidal anti-inflammatory agents (NSAIDs). GI = gastrointestinal; CNS = central nervous system; COX-2 = cyclooxygenase-2. *As a group, with the exception of *aspirin*, these drugs may have the potential to increase risk of myocardial infarction and stroke.

Questions

MCQs:

1-A five years boy was brought to the ER by his older brother complaining from runny nose and severe headache. Which of the following drugs can be used with this patient?
A)Aspirin
B)Paracetamol
C)Diclofenac

2-The bronchospasm effect of NSAIDs is due to
A)Stimulation of COX
B)Overproduction of Prostaglandin
C)Lipoxygenase effect

3-The possible cause of Acute renal failure mediated by Paracoxib is
A)Water retention
B)Vasoconstriction of afferent and efferent blood vessels
C)Stimulation of PGE2

4-A 67 years old lady was found dead in her home. At autopsy , it was found that her liver is pale and full of fibers. Refining her medical records it was found that she had peptic ulcers and asthma. Which of the following could be the reason behind the damaged liver?
A)Overdose of Acetaminophen
B)Using N-acetylcysteine
C)Aspirin

5-Celecoxib is contradicted with what?
A)Asthmatic patients
B)Chronic heart disease
C)Sulphonamides allergy

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

Cont..

SAQ:

A woman complaining from migraine was prescribed Ibuprofen. Based on those information, answer the following:

A-Mention the class and the mechanism of action of Ibuprofen

Nonselective COX-1 and COX-2 inhibitor

B-In brief, talk about the possible cause of pain in this patient

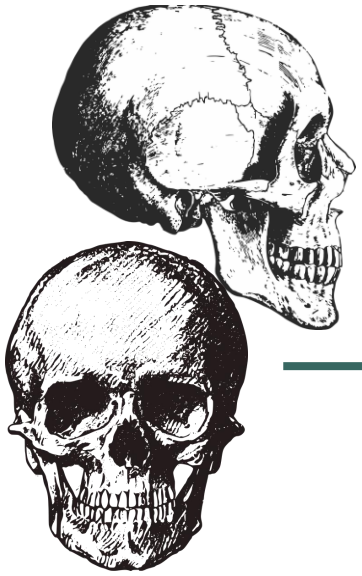
PGE2 and PGF2 are released in the brain tissue to stimulate pain receptors which causes the pain sensation in migraine.

C-Mention 3 ADRS of this drug

1-GIT upsets
2-Bleeding
3-water and salt retention

D-What protective effect does this drug have?

Cardioprotective effects by inhibiting the formation of thrombosis



"It is not hard, you just made it to the end!"

Team Leaders:

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شكرًا جزيلًا للزميلة **لين التميمي** من دفعة 436 على تعاونها اللطيف و نصائحها الغنية لإتمام هذا العمل.

References:

- ✓ Team436
- ✓ Doctors' notes and slides

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