PHARMACOLOGY
433

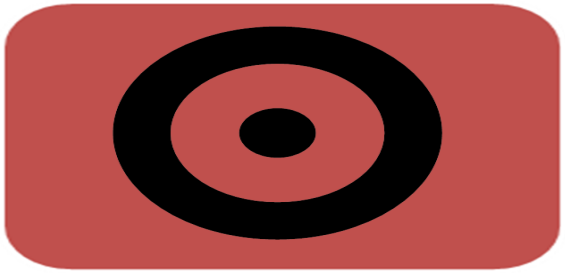
King Saud University
College of Medicine
1st Year, 2nd block

NSAIDs 2

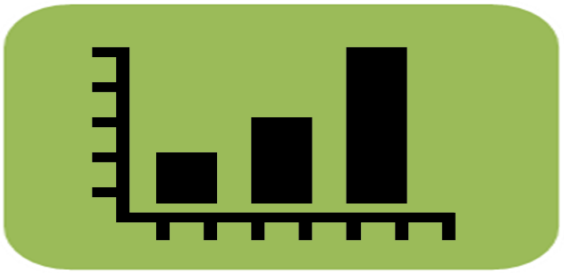
Non-Steroidal Anti-Inflammatory Drugs

Musculoskeletal Block

OBJECTIVES

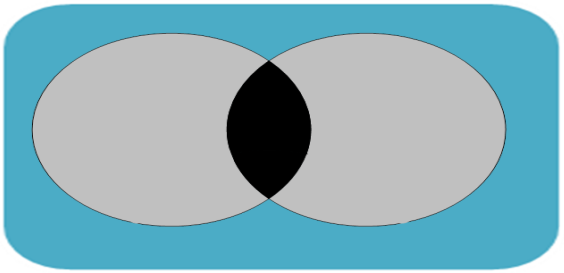


Define, classify, and describe the mechanism of action of NSAIDs

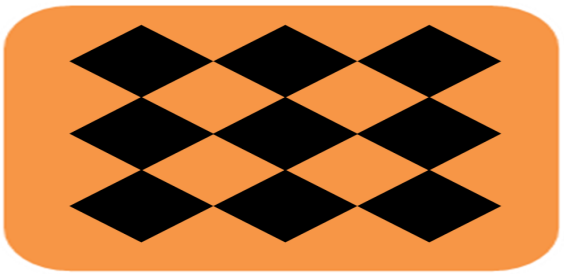


Define the terms: Analgesic, Antipyretic, Anti-inflammatory and Anti-platelets

Describe the general :
pharmacological actions, therapeutic uses, adverse affects and contraindications



Know some examples of each group of NSAIDs



Know the difference between the selective & non-selective NSAIDs

Classification of NSAIDs :

*Non-selective COX1/2 inhibitor:

-Aspirin
-Diclofenac
-Ibuprofen
-Indomethacin

COX-3 inhibitors : Antipyretic analgesics
ex: Paracetamol
مثال على COX inhibitors وليس NSAIDs

*Selective COX2 inhibitor:

-Celebrex = Celecoxib
-Vioxx
-Arconixa

Pharmacological actions:

*Analgesic : relieve pain that is mediated by prostaglandins
*Antipyretic : lower the elevated body temperature to normal(1)
*Anti-inflammatory
*Anti-platelets : No coagulations
*Effect on the kidney functions. "side effect of NSAIDs, when used chronically"

Pharmacokinetics:

***Absorption**: most are administrated **orally**, and are **weak acid** absorbed best in stomach and intestinal mucosa
***Distribution**: 95% are bound to plasma-protein → **high bioavailability.**
***Metabolism**: in liver "oxidation and conjugation reactions"
***Excretion:** by the Kidney.

Medical Tip

(1): the difference between hypothermia and antipyretic
Hypothermia: decrease the normal body temperature to **below the normal.**
Antipyretic: Drug that lower the elevated body temperature to normal. But, if we take it in normal temperature it won't affect. WHY? Because aspirin inhibits the synthesis of Prostaglandins which is the reason of the high temp.

Mechanism of action of NSAIDs :

inhibit COX 1 and 2 enzymes that are synthesized by Arachidonic acids

which will inhibit the synthesis of prostaglandins

General Mechanism of Action Of NS-NSAIDs

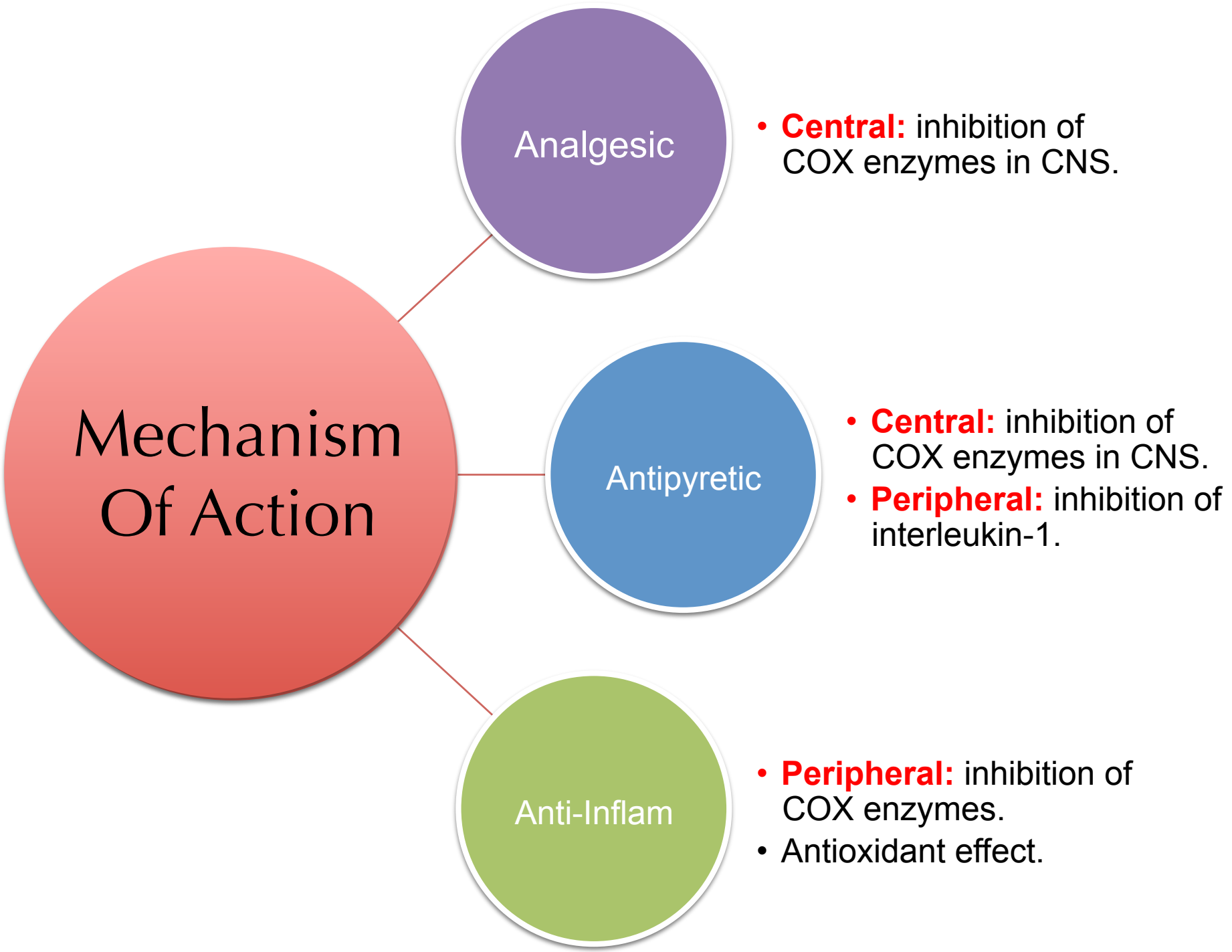
Reversible inhibition of both COX-1 & COX-2 enzymes

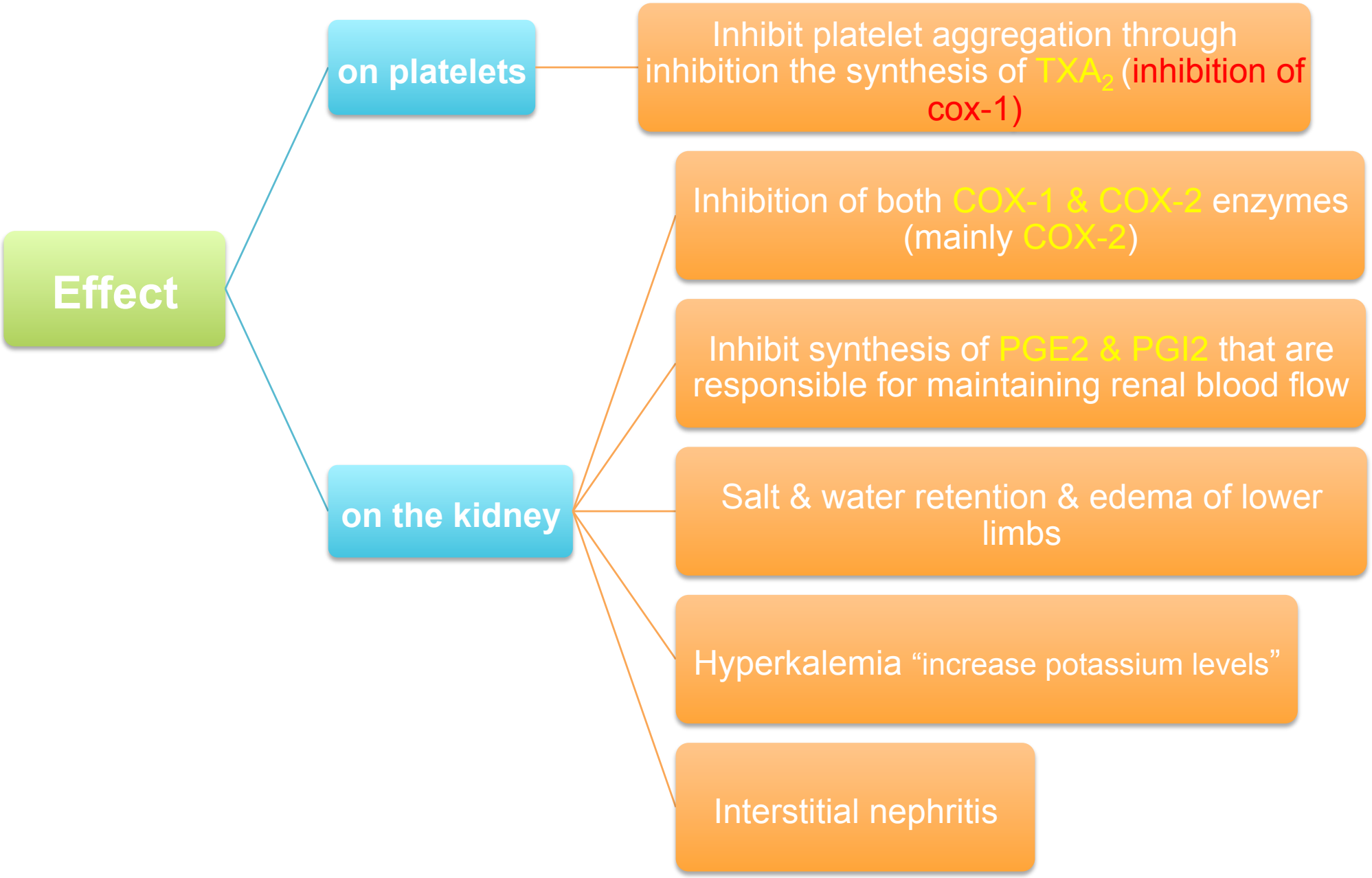
EXCEPT Aspirin is the only NS-NSAID that irreversible inhibitor of both enzymes

Resulting in inhibition of the synthesis of prostaglandins & thromboxane A2

Medical Tip

*If a patient is taking Aspirin and going to have a surgery, he should stop it 7 days before the surgery because Aspirin has an irreversible affect on platelets, so the bleeding will be prolonged.


Mechanism Of Action
Analgesic
• Central: inhibition of COX enzymes in CNS.
Antipyretic
• Central: inhibition of COX enzymes in CNS.
• Peripheral: inhibition of interleukin-1.
Anti-Inflam
• Peripheral: inhibition of COX enzymes.
• Antioxidant effect.


Effect
on platelets
Inhibit platelet aggregation through inhibition the synthesis of TXA_2 (inhibition of cox-1)
on the kidney
Inhibition of both COX-1 & COX-2 enzymes (mainly COX-2)
Inhibit synthesis of PGE2 & PGI2 that are responsible for maintaining renal blood flow
Salt & water retention & edema of lower limbs
Hyperkalemia "increase potassium levels"
Interstitial nephritis

NS-NSAIDs

e.g. : Aspirin, Diclofenac

*Pharmacological actions :

-Antipyretic.

-Analgesic : Dull "indescribable pain", mild and moderate pain e.g. headache, migraine, dental pain and common cold.

-Anti-inflammatory : Rheumatic, Rheumatoid arthritis, myositis or other forms of inflammatory conditions.

-Dysmenorrheal : because the prostaglandin increases the uterine contraction.

*Adverse Effects :

-GIT upsets : nausea, vomiting.
-GIT bleeding & ulceration. : that's why we never take them on empty stomach.
-Bleeding.
-Hypersensitivity reaction.
-Inhibition of uterine contraction.
-Salt & water retention : causes edema

Medical Tip

*uterine contractions inhibition is a side effect for pregnant women during labor. So women before labor should avoid NS-NSAIDs.

Aspirin

"other name: Acetyl salicylic acid, irreversible inhibition of COX, long duration of action, antioxidant"

Clinical uses

-Acute rheumatic fever

-Prevention of pre-eclampsia.

-Low doses : cardio-protective to reduce the incidence of\ *myocardial infarction *unstable angina.

-Large doses : (5gm) treats chronic gouty arthritis. "because it increase excretion of uric acid"

-Chronic use : small doses are used as protective to reduce the incidence of colorectal cancer. "because aspirin has potent antioxidant activity"

Adverse reactions

1.Theraputic doses :

-Nausea & vomiting

-Hypersensitivity :Aspirin asthma(1)

-Acute Gouty arthritis

-Reye's syndrome.(2)

-Impaired haemostasis

-mucosal damage→ hemorrhage.

2.Large doses or chronic uses "changes the mechanism of action of Aspirin":

-Salicylism : ringing of ear, tinnitus, vertigo.

-Hyperthermia.

-Gastric ulceration and bleeding.

-Respiratory depression.

Contraindications

"when Aspirin cannot be used"

-Peptic ulcer

-Pregnancy

-Hemophilic patients

-Patients taking anticoagulants

-Children with viral infections

-Gout (small doses)

Medical Tip

(1) : To differentiate between Aspirin asthma and Bronchial asthma, we can take a look at the patient's history, because they both have the same symptoms: difficulty in breathing, if he was taking Aspirin, this means it's Aspirin asthma.

(2) :Happens when a patient infected by a virus and has fever and takes Aspirin. Occurs more in children.

Diclofenac

"reversible inhibition, accumulate in synovial fluid, anti-inflam. drug"

Clinical uses	Preparations
-Rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. -Analgesic. -Antipyretic. -Acute gouty arthritis "all NSAIDs treat it except Aspirin" -Locally to prevent post-opthalmic inflammation.	-Oral -Oral with misoprostol to decrease upper gastrointestinal ulceration. "remember that misoprostol is an analog prostaglandins that treats peptic ulcer" -Oral mouth wash. -Eye drops to decrease postoperative ophthalmic inflammation. (0.1%) -Topical gel (3%) -Rectal suppository -Intramuscular preparations.

Selective COX-2 inhibitors

General advantages	General adverse effects	GENERAL CLINICAL USES	Example
▪Potent anti-inflammatory ▪Antipyretic & analgesic ▪Lower incidence of gastric upset **(recommneded in patients with a history of gastric ulceration)** ▪No effect on platelet aggregation (have no inhibitory effect on (COX-1 enzyme) so can be given in hemophilic patients)	•Renal toxicity •Dyspepsia & heartburn •Allergy •Increase incidence of myocardial infarction (lack cardioprotective effect of NS-NSAIDs as they have no effect on COX-1 enzyme)	**Commonly used as antiinflammatory drugs** ▪Rheumatoid arthritis ▪Osteoarthritis ▪Acute gouty arthritis ▪Acute musculoskeletal pain ▪Ankylosing spondylitis ▪Dysmenorrhea	**Celecoxib:** • Half-life 11 hours (twice/day) • Food decrease its absorption • Highly bound to plasma proteins ○ **Clinical uses & Adverse effects :** Discussed before with general uses and general adverse effects of selective COX-2 inhibitors. ○ **Drug interactions :** With **warfarin** (anticoagulant) celecoxib inhibits warfarin metabolism so it potentiates its action resulting in bleeding.

Paracetamol

"reversible inhibition, used as analgesic and antipyretic, weak in infalm. conditions because it acts on the central NS"

given orally , well absorbed, peak plasma concentration reached in 30-60min , variable proportion is bound to plasma protein

Drug is inactivated in the liver, conjugated with glucuronic & sulphuric acid ,t½=2-4h.

Clinical uses	Adverse reactions (Due to its active metabolite)
In patients with : -Peptic or gastric ulcers. -Bleeding tendency. -Allergy to aspirin. -Viral infections especially in children . -During Pregnancy "it's the safest drug during pregnancy" It is usually used when Aspirin is contraindicated.	**Mainly on liver due to its active metabolite** **(N-acetyl-p-benzoquinone)** **Therapeutic doses :** -Elevate liver enzymes. -Chronic administration causes kidney failure "necrosis". Large doses : -Acute toxicity : "liver failure (necrosis)" [Treatment of acute toxicity is by : N- acetylcysteine (SH- donor) to neutralize the toxic metabolite]

Summary

❖ **Define NSAIDs**

NSAIDs stands for = Non-Steroidal Anti-Inflammatory Drugs.

Describe the general mechanism of actions
+ Describe the classification of this group of drugs
+ Know the difference between the selective & non-selective NSAIDs
+ Know some examples of each group of NSAIDs

Generally; these drugs work on the COX enzyme family
- Non-Selective NSAIDs: They reversibly Inhibit COX1 & COX2 (mainly 2)
EXCEPTION: Aspirin (Irreversible inhibitor)
Examples: Aspirin, Paracetamol and Diclofenac.

- Selective NSAIDs: inhibit only COX-2 enzymes
NOTE: No effect on COX1 = Can be given to hemophilic patients
Example: Celecoxib

❖ **Describe the general therapeutic uses**
Analgesic = pain reliever drugs
Antipyretics = Drugs that lower the body temperature to normal.
Anti-Inflammatory
Dysmenorrhea

v **Describe the general adverse effects**
- Effects on the GIT: Nausea, vomiting, bleeding and ulceration.
- Hypersensitivity reaction.
- Inhibition of uterine contraction (Prolongs labor) ☹
- Salt and water retention.

v **Describe the general contraindications**
Mainly; Patients with peptic ulcer, and Hemophilic patients or in pregnancy.

MCQs

2. A drug could have a local effect?
a.Paracetamol.
b.Aspirin.
c.Dicolofenac.
d.Celecoxib.

3. The main root of excretion of the NSAID's is :
a.Liver.
b.Kidney.
c.Lungs (exhalation).
d.Sweat Gland (sweating).

4.The peripheral effect of Antipyretic :
a.Inhibition of cox enzymes in CNS.
b.Antioxidant effect.
c.Inhibition of interleukin-1.
d.All of the above.

5.A 6-year old boy has and inflection and he suffer from dental pain what should NOT you give him ?
a.Paracetamol.
b.Aspirin.
c.Small doses of Panadol.
d.Dicolofenac (voltaren).

6.A patient with acute gouty arthritis, should be prescribed by:
a.Dicolofenac.
b.Small doses of Aspirin.
c.Oral Aspirin.
d.Paracetamol.

7.A patient with heart disease came suffering from headache what should you prescribe him?
a.All kind of NSAID's.
b.Selective NSAID's (cox2 inhibitor).
c.Celecoxib.
d.Aspirin.

8.A girl has Dysmenorrhea she need to take :
a.Selective NSAIDs.
b.Non Selective NSAIDs.
c.All of the above.
d.None of the Above.

9.A patient with gastric ulceration with fever, the best drug for him is:
a.Celecoxib.
b.Aspirin.
c.Dicolofenac.
d.None of them.

10.A patient with kidney failure has a dull pain what should you give him?
a.Selective NSAID's.
b.None Selective NSAID's.
c.All of the above.
d.None of the above.

2:C, 3:B, 4:C, 5:B, 6:A,
7:D, 8:C, 9:A, 10: D

We hope we made this lecture easier for you
Contact us for any questions or comments
Good Luck !

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