MED438
KING SAUD UNIVERSITY

pharmacology
Team 438

- Red : important
- Black : in male / female slides
- Pink : in female's slides only
- Blue : in male's slides only
- Green : Dr's notes
- Grey: Extra information, explanation

Editing File

LECTURE 1: 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.

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%.

what are NSAIDs?

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are group of drugs that share in common the capacity to induce the following effects:

NSAIDs effects

Anti-inflammatory

When there is an inflammation, Prostaglandins + bradykinin and histamine and 5HT "serotonin" initiate the symptoms of INFLAMMATION: (Redness, swelling, heat, pain, and sometimes loss of function).
NSAIDs anti-inflammatory mechanism: block PGs production
Site of action: peripheral tissues

clinical uses:

• Rheumatoid arthritis / Myositis* inflammation and degeneration of muscle tissue.
• Common cold

Antipyretic (reduce fever)

Pyrogens (substances typically produced by bacteria or virus) stimulate formation of Prostaglandins, which then increases 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.

Analgesic (painkiller)

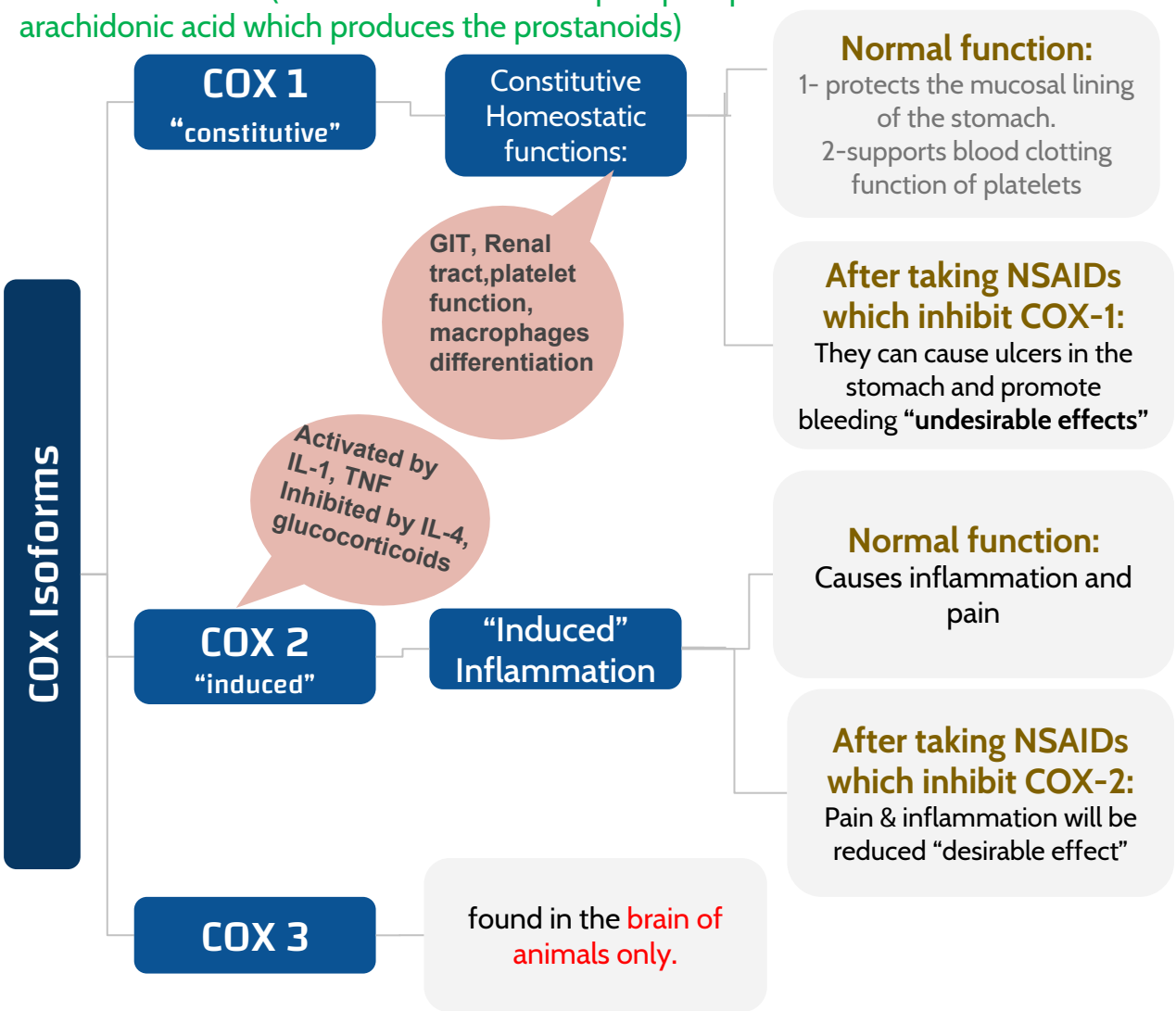
Prostaglandins + bradykinin and histamine at the site of the injury normally sensitize pain sensors at the nociceptors found at nerve endings to produce PAIN.
NSAIDs analgesics mechanism: block PGs production.
Site of action: peripheral tissue

clinical uses:

• Headache, Migraine* headache that affects one side of the head
• Dysmenorrhea* painful menstruation and abdominal cramps
• Dental pain (moderate pain).

Mechanism of action of NSAIDs:

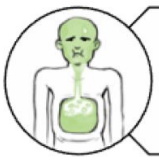
Inhibition of CycloOxygenase (COX) enzyme which leads to the inhibition of Prostanoids (Thromboxane,Prostacyclin, Prostaglandin) synthesis which promotes inflammation, pain and fever. As a consequence, ongoing inflammation, pain and fever are reduced < All actions and side effects are due to this inhibition. (Corticosteroids inhibits phospholipase A2 and the formation of arachidonic acid which produces the prostanoids)



Classification of COX inhibitors :

Type	Example
Nonselective (inhibits COX-1&2)	Aspirin, Diclofenac, Ibuprofen, Naproxen
Selective COX-2 (inhibits only COX-2)	Coxibs
Preferential COX-2 inhibitors (Prefers inhibiting COX-2 more than COX-1)	Meloxicam
COX-3 inhibitors	Paracetamol

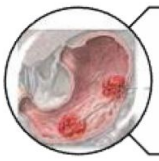
ADRs (Adverse drug reactions):



GIT upsets (nausea, vomiting) thus shouldn't be consumed on empty stomach

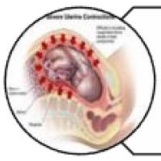
Hypersensitivity reactions

Inhibition of PGs leads to inducing leukotrienes



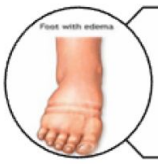
GIT bleeding & ulceration

By inhibiting Cox1 which protect the lining of the stomach from the damaging acids



Inhibition of uterine contraction

By inhibiting Prostaglandins, which induce labor.

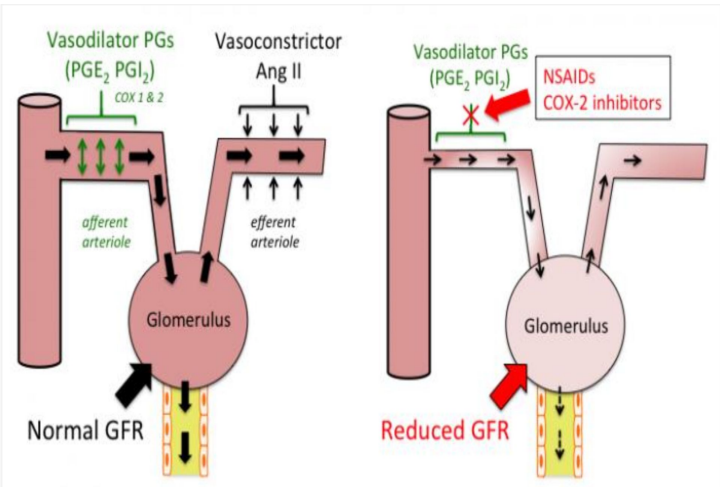


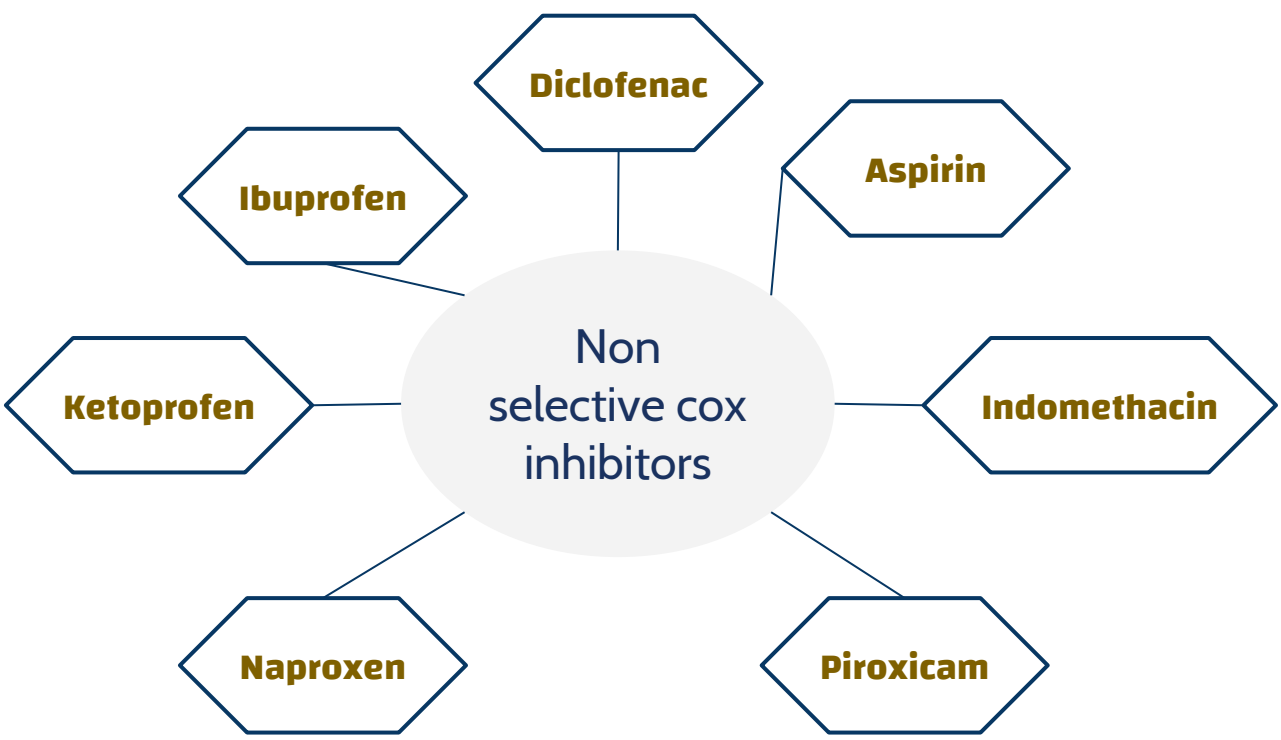
Salt & water retention

Explained below↓

Renal ADRs:

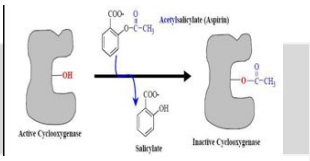
NSAIDs cause hemodynamically-mediated acute renal failure.They prevent the synthesis of PGE2 & PGI2 by inhibiting COX-1 & COX- 2 leading to the prevention of vasodilation, and reducing GFR(Glomerular filtration rate). COX-2 is found as a constitutive isoenzyme in the kidney.





Aspirin (Acetylsalicylate): Non selective COX1/COX2 inhibitor

Mechanism of action



Aspirin binds with the active site of COX enzyme and makes it inactive -acetylation- . (This process is irreversible) - Aspirin is the only one with that nature.

Pharmacokinetics

1. Higher dose of aspirin has a long plasma half- life.
Aspirin follows Zero-Order kinetics, which means a high dose of Aspirin will not be excreted which leads to accumulation in the body causing toxicity

Low dose: t1/2 = 3h. Higher dose: t1/2 = 15h.

2. Metabolized by hydrolysis and then conjugation.
   - Taking a salicylate "like aspirin" with antacid slows food absorption.
     (Antacids reduce acidity of stomach leading to dysfunctioning enzymes hence there will be slower food absorption)

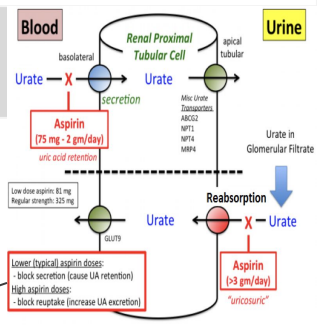
Clinical uses

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

Contraindications موانع الاستعمال

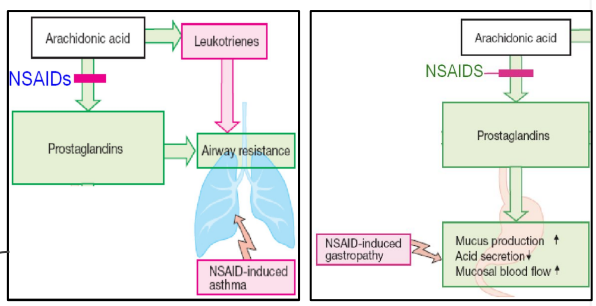
1. Peptic ulcer. 2. Patients taking Anticoagulants.
3. Hemophilic patients. 4. Children with viral infections.
(Reye's Syndrome) 5. Pregnancy. 6. Gout (at small doses).

red box is important



At clinical dose

- Hypersensitivity
- Acute gouty arthritis. Because of uric acid retention.
- Reye's syndrome. Affects children with viral infection who take aspirin.
- Impaired haemostasis. Bleeding
- GIT side effects, dyspepsia, nausea and vomiting
- Mucosal damage ---> hemorrhage
- Bronchospasm in aspirin- sensitive asthmatics



At overdose

1. Hyperthermia. The nutrients producing energy will be oxidized, but no ATP will be made so the energy of bond formation will act as heat throughout the body. .
2. Gastric ulceration and bleeding.
3. Salicylism (Ringing of ear, vertigo). Treated by stopping the administration of Aspirin.

Diclofenac (voltaren) Non selective cox1 / cox2 inhibitor

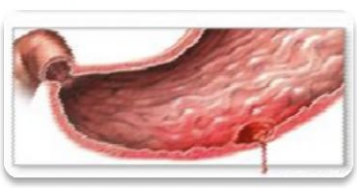
Mechanism of action

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

Clinical uses

1. Analgesic.
2. Antipyretic.
3. Anti-inflammatory. Strong effect.
4. Acute gouty arthritis. remember, this is one of the adverse effects of low doses of aspirin.
5. Locally to prevent postoperative ophthalmic inflammation (solution). (eye drops) for treating inflammation after operations on the eye. ophthalmic= related to the eye.

Preparation

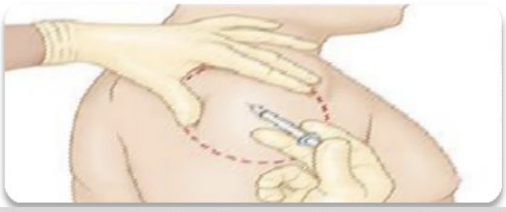


1. Diclofenac with **misoprostol** (a PGE1 analog) decreases upper gastrointestinal ulceration, but results in diarrhea.

2. Diclofenac with **omeprazole** to prevent 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 over many years.



5. Oral mouth wash.
6. Intramuscular preparations for pain & fever .
7. Rectal suppository as analgesic.

selective cox-2 inhibitors (Coxibs): 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's withdrawn because of risk of myocardial infarction and stroke

General action

1. Potent anti-inflammatory.
2. Antipyretic & analgesic.
3. Lower incidence of gastric upset.
4. No effect on platelet aggregation(COX-1) No cardioprotective effect.

General ADRs

1. Renal toxicity
2. 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.
3. Dyspepsia & heartburn. it is not as potent as the one caused by COX-1 inhibitors
4. Allergy

Clinical uses

1. Short-term use in postoperative 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)

contraindications موانع الاستعمال

Shouldn't be given to a patient with CV diseases

cox-2 inhibitors (selective, preferential):

Drug	Celecoxib	Meloxicam, Nimesulide, Nambumetone
P.K	1. Half-life 11 hours 2. Food decreases its absorption (Not given with food) 3. Highly bound 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 it becomes non-selective in the case of an overdose
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.	-

More damaging

Less damaging

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

Paracetamol (acetaminophen): Cox-3 inhibitors (does NOT belong to NSAIDs)

General features

1. COX-3 selective inhibitor.
2. Given orally, well absorbed.
3. t½ =2-4 h
4. Metabolized by conjugation at therapeutic doses.
5. Weak anti-inflammatory effect. It is not given in conditions associated with inflammation.

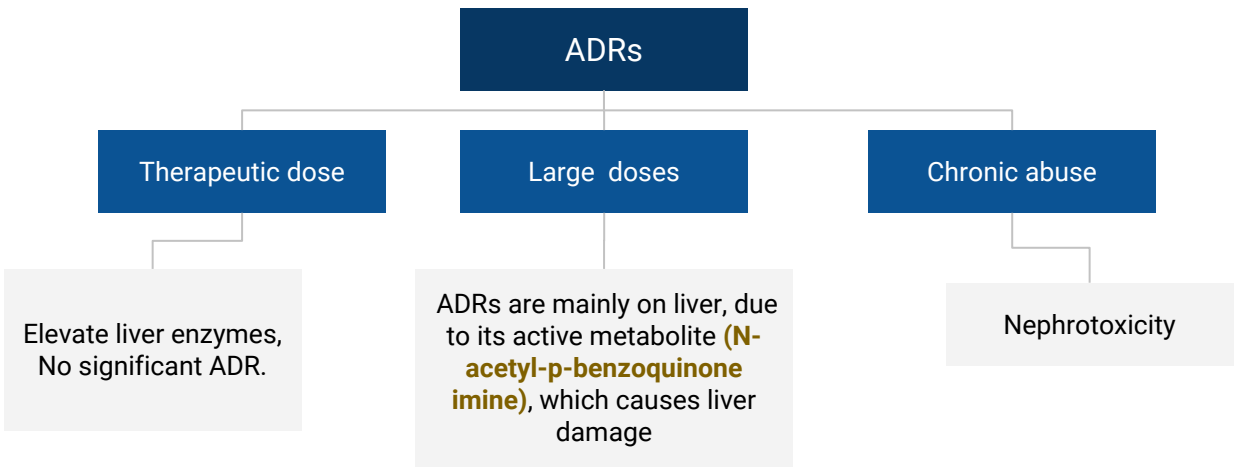
Clinical uses

Commonly used analgesic antipyretic instead of aspirin in cases of:

1. Peptic or gastric ulcers
2. Pregnancy
3. Viral infections in children
4. Bleeding tendency
5. Allergy to aspirin

REMEMBER:
aspirin can't be used in these cases.
1. An ADR of aspirin is peptic ulcer, therefore, consuming it by patients who already suffer from gastric ulcer will make it worse.
2. Can't be used by pregnant women because of its defects on the fetal cardiovascular system.
3. aspirin + kids with viral infections = Reye's syndrome.
4. aspirin also causes impaired hemostasis and leads to bleeding tendency.
5. it also causes hypersensitivity reactions.

Adverse Drug Reactions



-Treatment of toxicity of paracetamol is by N- acetylcysteine to neutralize the toxic metabolite. (This molecule binds to Paracetamol active metabolites before they reach Sulfhydril 'SH' in tissues to cause cytotoxicity, N-acetylcysteine neutralizes the active metabolite 'N-acetyl-p-benzoquinone imine' to stop that process.)
-Binding of paracetamol to COX is inhibited by peroxides produced in inflammatory sites, there's no evidence that COX3 exists in humans. Found in animals only.

QUIZ

Quiz (MCQ) :

Q1.Which one of these COX Isoforms found in the brain?

A)COX-1 B)COX-2 C)COX-3

Q2.Meloxicam is an example of?

A)COX-3 inhibitors B)Preferential COX-2 inhibitors C)Selective COX-2

Q3.Which one of these drugs consider as a cardioprotective drug ?

A)Celecoxib B)Acetylsalicylate C)Atropine

Q4.Which one of these drugs shouldn't be taken by patients with Sulphonamides allergy?

A)Celecoxib B)Acetaminophen C)Rofecoxib

Q5. 7 years old child with a high fever associated with a viral infection , what is the suitable antipyretic drug for him ?

A)Acetylsalicylate B)Aspirin C)Acetaminophen

ANSWER : 1)C - 2)B - 3)B - 4)A - 5)C

Quiz (SAQ) :

Q1.Define the NSAIDs?

Q2.What is the mechanism of action of the NSAIDs ?

Q3.Patient was taking anti- inflammatory drug for a long time, he came to the emergency with severe pain. The diagnosis was peptic ulceration. Which of the following drug he might be taking ?

Q4.Which drug can cause acute gouty arthritis ?

Q5.A 9 years old child have a history of viral infection and he was treated by taking NSAIDs ,after one week he came to emergency suffers from confusion, seizures and loss of consciousness he also have swelling in the liver and brain.The diagnosis was (Reye's syndrome).Which of the following NSAIDs he might have?

Q6.What are the common GIT side effects of NSAIDs ?

7-8: 64 years old man complaining from a pain in his joint that limit his movement , after examination the diagnose is rheumatoid arthritis.

Q7.Which drug is suitable to prescribe to his condition ?

Q8.What is the class and the mechanism of action of that drug?

9-10.A patient came to the emergency with abdomen pain , the examinations show a hepatotoxicity.

Q9.What is the possible cause of his condition ?

Q10.What is the suitable treatment of this condition ?

QUIZ

1.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

2.Inhibition of Cyclo Oxygenase (COX) enzyme

3.Nonselective COX1/COX2 inhibitors

4.Small dose of aspirin.

5.Aspirin

6. GIT upsets (nausea, vomiting) - GIT bleeding & ulceration

7.Meloxicam

8. Preferentially inhibits COX-2 over COX-1

9.large doses of Paracetamol

10.N-acetylcysteine

pharmacology

Team 438

GOOD LUCK

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