Pharmacology team 436

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MEDICINE 436 KING SAUD UNIVERSITY

NSAID: Non-Steroid Anti-Inflammatory Drugs

Objectives:

- Action of NSAIDs
- Effects of and ADRs of NSAIDs
- NSAIDs and COX enzyme
- Pharmacokinetic properties and pharmacodynamic effects of selected NSAIDs

قد يكون السطر الذي حرم عينيك النوم ليلة,
شفاء لداء ارق العليل ليال طوال...
خلقت بلسما فلا تشتكي

- Titles
- Very important
- Extra information
- Terms

Prostaglandins actions (extra)

- cause constriction or dilation in vascular smooth muscle cells.
- cause aggregation or disaggregation of platelets (COX1) .
- induce labor by increasing smooth muscles contraction
- regulate inflammation.
- acts on thermoregulatory center of hypothalamus to produce fever.
- increase glomerular filtration rate.

So for example inhibiting COX1 will decrease blood coagulation, which is sometime desirable when there is a cardio problem or for diabetic patients, and sometimes not, cause it my lead to excessive bleeding.
Also it will increase gastric acid secretion that causes damage of the gastric mucosa which leads to gastric ulcer.

COX-1	COX-2
Blood clotting	Mediate inflammation
protects gastric mucosa	Pain

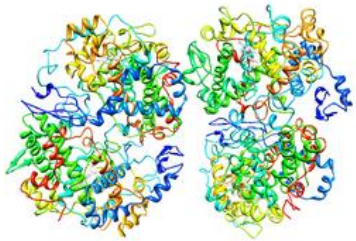
Non-steroidal anti-inflammatory Drugs

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.

COX isoforms :

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

COX-1
&
COX-2



Actions of NSAIDs

Blocking of PGs production results in :

1. **Analgesic**

   افف (EF) الألم (PAIN) مرره يوجع

   NSAIDs inhibit the formation of PGE2 & PGF2 causing **analgesia** (pain killer) in **peripheral tissue**.

2. **Antipyretic**

   لما الدكتور يسأل عندك حرارة(FEVER) ونجاوب أي (E) عندي حرارة

   NSAIDs inhibit the formation of PGE2 which activates the thermoregulatory center to raise Heat production and inhibit dissipation (**Fever)** in **CNS**.

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**.

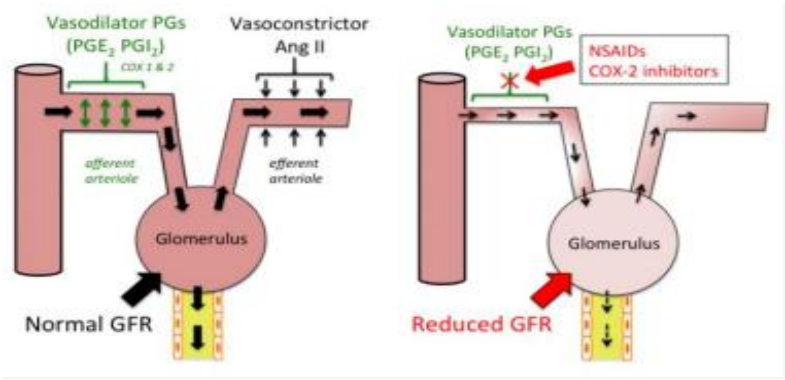
Clinical uses :



- Fever
- Headache, Migraine (صداع نصفي)
- Dental pain, Dysmenorrhea (painful periods)
- Common cold
- Rheumatoid arthritis / myositis

General ADRS

- GIT upsets (nausea, vomiting) mostly caused by non selective.
- GIT bleeding & ulceration.
- Bleeding.
- Hypersensitivity reactions Leukotriene cause hypersensitivity .
- Inhibition of uterine contraction.
- Salt & water retention.
- Impairment of kidney function.
- Hemodynamically mediated acute renal failure.



K(I)DN(E)Y = PGI2 & PGE2 for renal function

Examples:

1-Aspirin. 2-Diclofenac. 3-Ibuprofen.
4-Ketoprofen. 5-Naproxen. 6-Piroxicam.
7-Indomethacin.

❖Aspirin

Mechanism of action :

Inhabit COX (non selective) irreversibly.

Pharmacokinetics :

1. Higher dose of aspirin has a long plasma half- life.
2. Metabolized by hydrolysis and then conjugation.

Clinical uses :

1. Acute rheumatic fever.
2. Reducing the risk of myocardial infarction (cardioprotective).
3. Prevention of pre-eclampsia*.
4. Chronic use of small doses reduce the incidence of colon cancer.

*Pre-eclampsia: a condition in pregnancy characterized by high blood pressure, sometimes with fluid retention and proteinuria.

Clinical dose	Hypersensitivity bronchospasm, rhinitis, conjunctivitis, urticaria
	Acute gouty arthritis (low doses)
	Reye's syndrome
	Impaired haemostasis
	GIT side effects, dyspepsia, nausea and vomiting
	Mucosal damage→ hemorrhage
Overdoes	Salicylism (ringing of ear , vertigo)
	Hyperthermia
	Gastric ulceration & bleeding

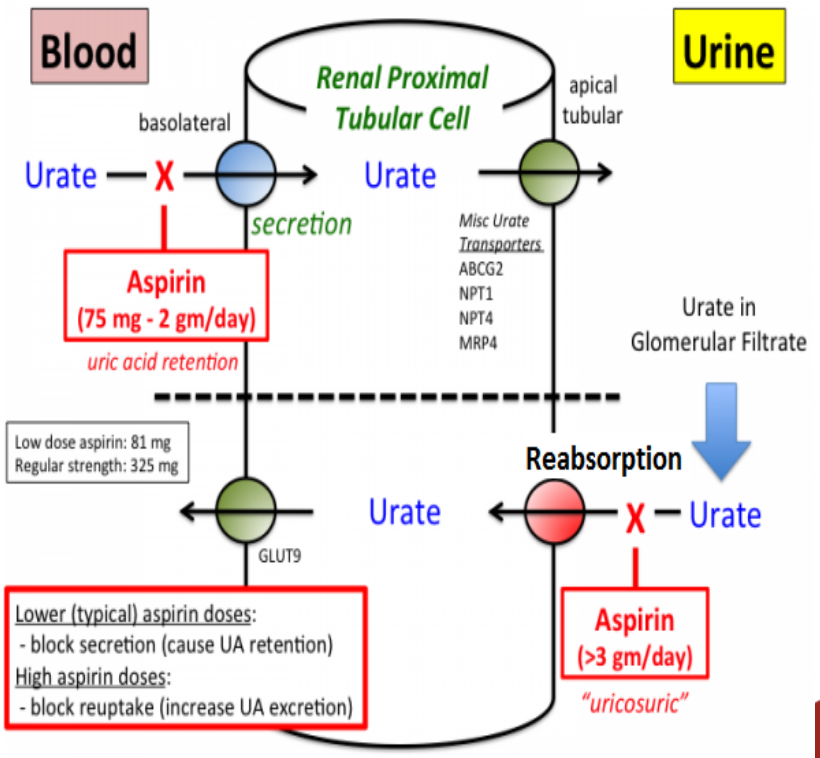
Reye's syndrome: is a rare but serious condition that causes swelling in the liver and brain.

Contraindications

Contraindications of Aspirin

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

*__Aspirin__ should be avoided during the third trimester due to possible premature **closure of the ductus arteriosus**



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
Uricosuric
Treat GOUT.

❖ Diclofenac

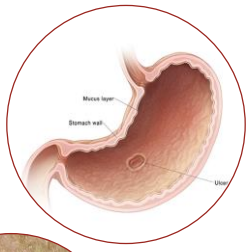
Clinical uses :

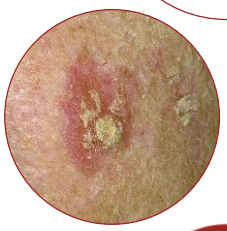
1. Analgesic.
2. Antipyretic.
3. Anti-inflammatory.
4. Acute gouty arthritis.
5. Locally to prevent post-operative ophthalmic inflammation.

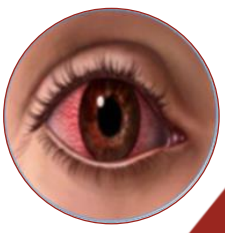
بالمصري نقول دي(di) كلو (clo) فينك(fenac) عنها بتسبب(ulcération & bleeding) so it is
non-selective act on COX-1

Preparations :

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







Selective COX-2 inhibitors

Examples:

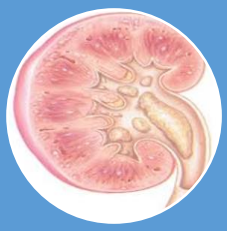
1-Celecoxib. 2-Etoricoxib. 3-Paracoxib.
5-Rofecoxib*. 6-Valdecoxib*.

*5+6 Withdraw 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).

General ADRs :



Renal toxicity

Cardio vascular

Dyspepsia & heartburn

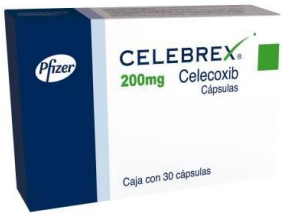
Allergy

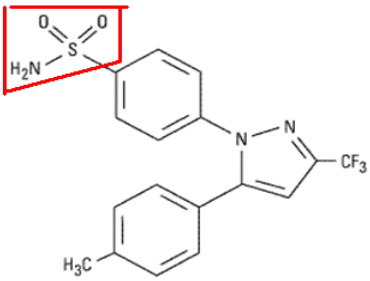
do not offer the cardio-protective effects of non-selective group. (not anti-platelet).

GENERAL CLINICAL USES

1. Short-term use in postoperative patients.
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)

Celecoxib





Celecoxib

- Half-life 11 hours.
- Food decrease its absorption (no gastric upset).
- Highly bound to plasma proteins.

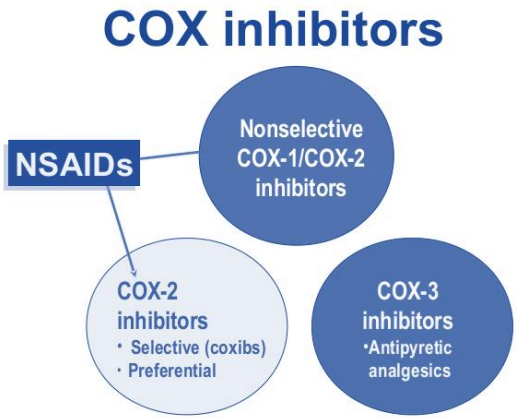
Preferential COX-2 inhibitors

Examples:

1- meloxicam. 2-nimesulide. 3-nambumetone.

- Preferentially inhibit COX-2 over COX-1. particularly at low dose.
- Associated with lower GIT symptoms and complains, compared to non-selective COX inhibitors
- T ½ = 20 hours.
- Used for:
    1. Osteoarthritis.
    2. Rheumatoid arthritis.

Paracetamol (selective COX-3)



General information:

- Weak anti-inflammatory effect.
- Given orally , well absorbed.
- t½=2-4 h.
- Metabolized by conjugation at therapeutic doses.

COX-3 is an enzyme that is encoded by the *PTGS1* (*COX1*) gene, but is not functional in humans. COX-3 is the third and most recently discovered cyclooxygenase (COX) isozyme

Clinical uses of Paracetamol:

Commonly used analgesic antipyretic, for patients with contraindications to aspirin:-

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

Adverse drug reactions

Therapeutic doses

Elevate liver enzymes, No significant ADR.

Large doses

- ADRs are mainly on liver, due to its toxic metabolite (N-acetyl-p-benzoquinone imine), which causes liver damage
- Treatment of toxicity of paracetamol is by N-acetylcysteine to neutralize the toxic metabolite

Chronic abuse

Nephrotoxicity

Comparison

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 fever of viral infections
Pregnancy	Pregnancy
Allergy to aspirin	Gout (small doses)

SAQ 1

A 64 year old male present with mild to moderate musculoskeletal back pain after playing golf. He states that he has tried acetaminophen and it did not help. His past medical history includes diabetes, hemophilia and gastric ulcer.

Q1: Which is the most appropriate NSAID to treat this patient's pain?
Celecoxib or any NSAIDs act only in COX-2.

Q2: What its mechanism to reduce the pain ?
Block PGs production which will cause the pain such as PGE2 & PGF2.

Q3: Do you think this drug in the future will lead to thrombosis or bleeding ?
Actually NO , because it acts on COX-2 only and does not have any effect on platelet aggregation.

Q4: One of its clinical uses is the treatment of Acute gouty arthritis, list other NSAIDs could used also ?
Diclofenac or Aspirin with large doses.

Q5: Why does this drugs have long half life? Its half life 11 hours.
Because it is highly bound to plasma proteins.

SAQ 2

A 13 year old girl has Acute rheumatic fever after streptococcal infection. She use Aspirin with high doses of 160 mg/kg/day, Aspirin is the drug of choice as anti-inflammatory in this case. Her medical history includes Salicylism .

Q1: What is the mechanism of Aspirin as anti-inflammatory drugs ?
Block PGs production which induces the inflammation such as PGE2 & PGF2.

Q2: What is the metabolite of Aspirin after hydrolysis in phase(I) ?
salicylic acid.

Q3: She has Salicylism, what symptoms do you think she has ?
Ringing in her ears, headache and vertigo.

Q4: Why we can not give hemophilic patients this drug ?
Because it is non-selective NSAIDs and inhibit both COX-1 & COX-2, and COX-1 is important for normal platelet function and aggregation.

Q5: What is the drug which commonly used analgesic antipyretic instead of aspirin in contraindications such as patient with GIT ulceration ?
Paracetamol (Acetaminophen)

QUIZ

Boys	Girls
عبدالرحمن ذكري	اللولو الصليهم
عبدالعزيز رضوان	روان سعد القحطاني
مؤيد أحمد	أثير الرشيد
فيصل العباد	سما الحربي
فارس النفيسة	نوره الشبيب
خالد العيسى	وتين الحمود
معاذ الفرحان	أمل القرني
عبدالرحمن الجريان	ابتسام المطيري
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