Non steroidal Anti-inflammatory drugs
NSAIDs L3, L4

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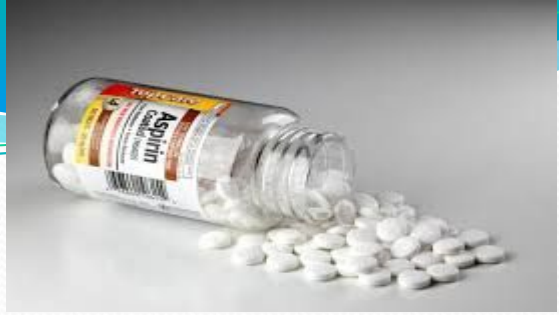
A. Nonselective COX inhibitors

Salicylates:



Aspirin

1- is a **weak organic** acid

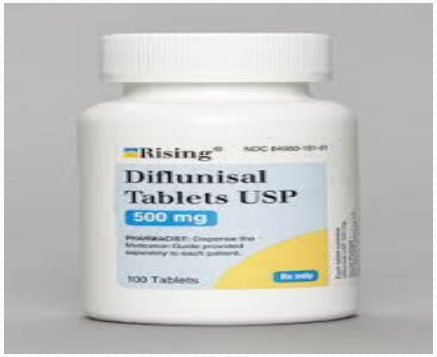
2- The **only** NSAIDs can **irreversibly** acetylating COX.

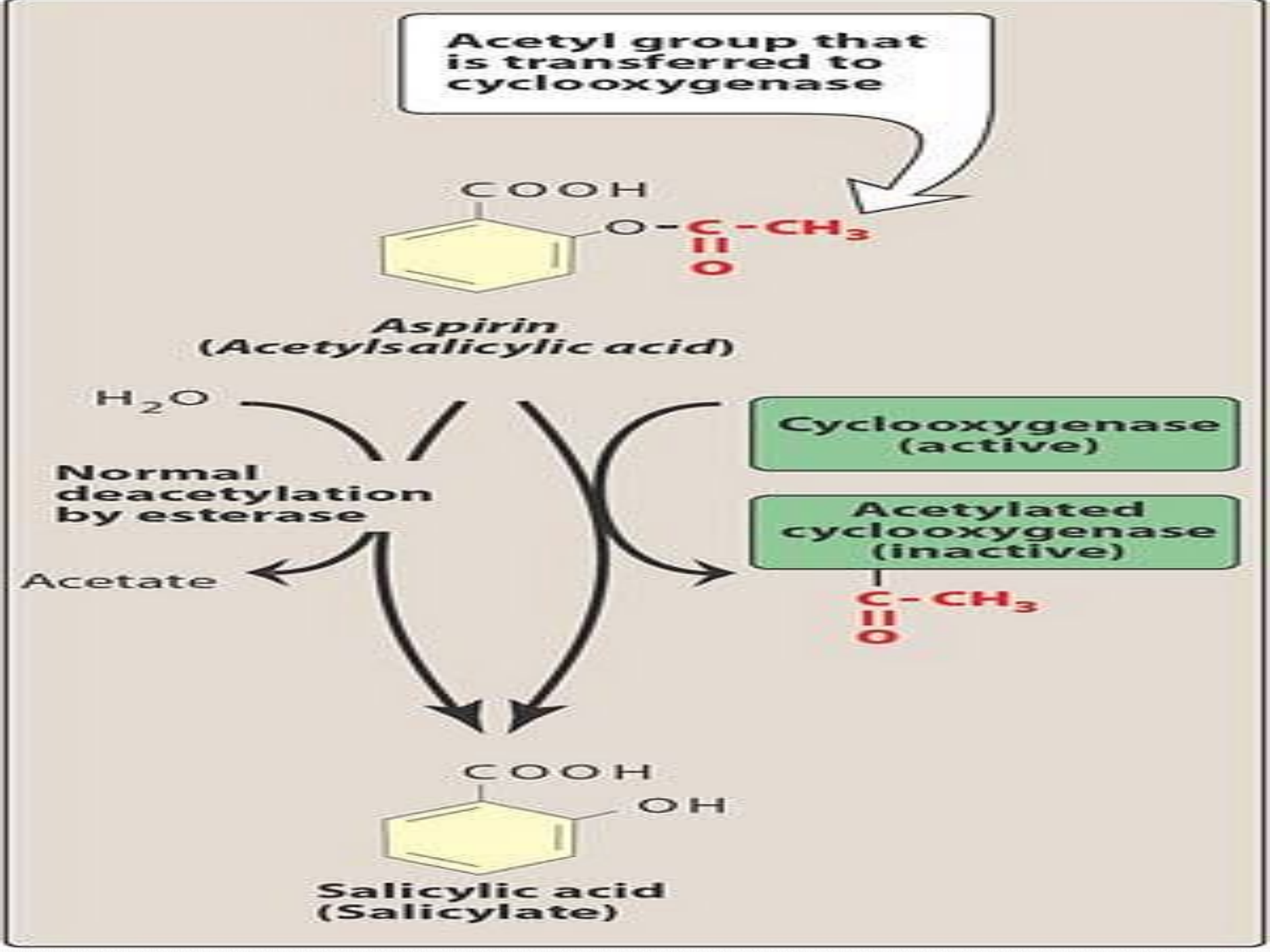
3- It is rapidly **metabolized** in the body by **esterase** to salicylates which has **anti-inflammatory**, **antipyretic** and **analgesic** effects.

4- **Absorbed** from **stomach** and **small intestine**.

5- **Excreted** by **kidney**.

6- **Slowly** enter the **brain**.




Acetyl group that is transferred to cyclooxygenase
COOH
O–C–CH3
O
Aspirin
(Acetylsalicylic acid)
H2O
Normal deacetylation by esterase
Acetate
Cyclooxygenase (active)
Acetylated cyclooxygenase (inactive)
C–CH3
O
COOH
OH
Salicylic acid
(Salicylate)

Diflunisal :is a derivative of salicylic acid

1- It does **not enter the CNS**.

2- It is **3-4** times **more potent** than aspirin as an **analgesic** and an **anti-inflammatory** agent.

3- It has **no antipyretic** effects (Not cross BBB)

Uses :-

1- Antipyretic, **anti-inflammatory** and **analgesics** (analgesic dose is **300-600 mg**).

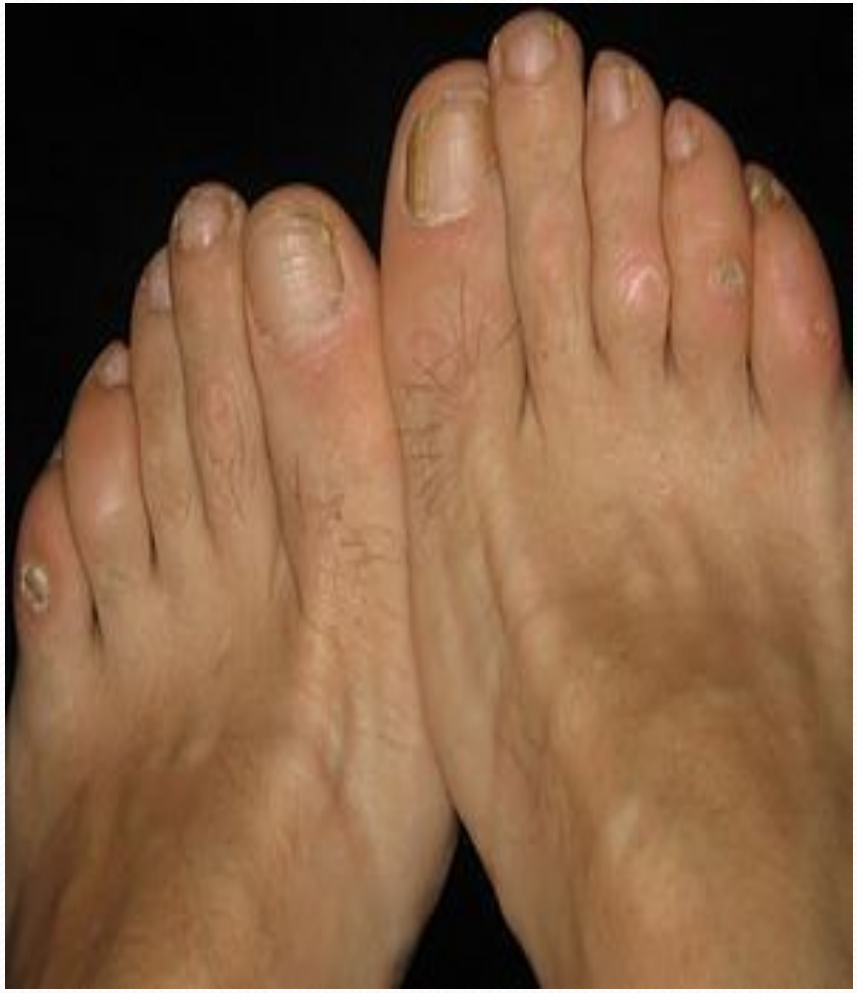
Aspirin is the drug of **1st choice** for acute **rheumatic fever**.

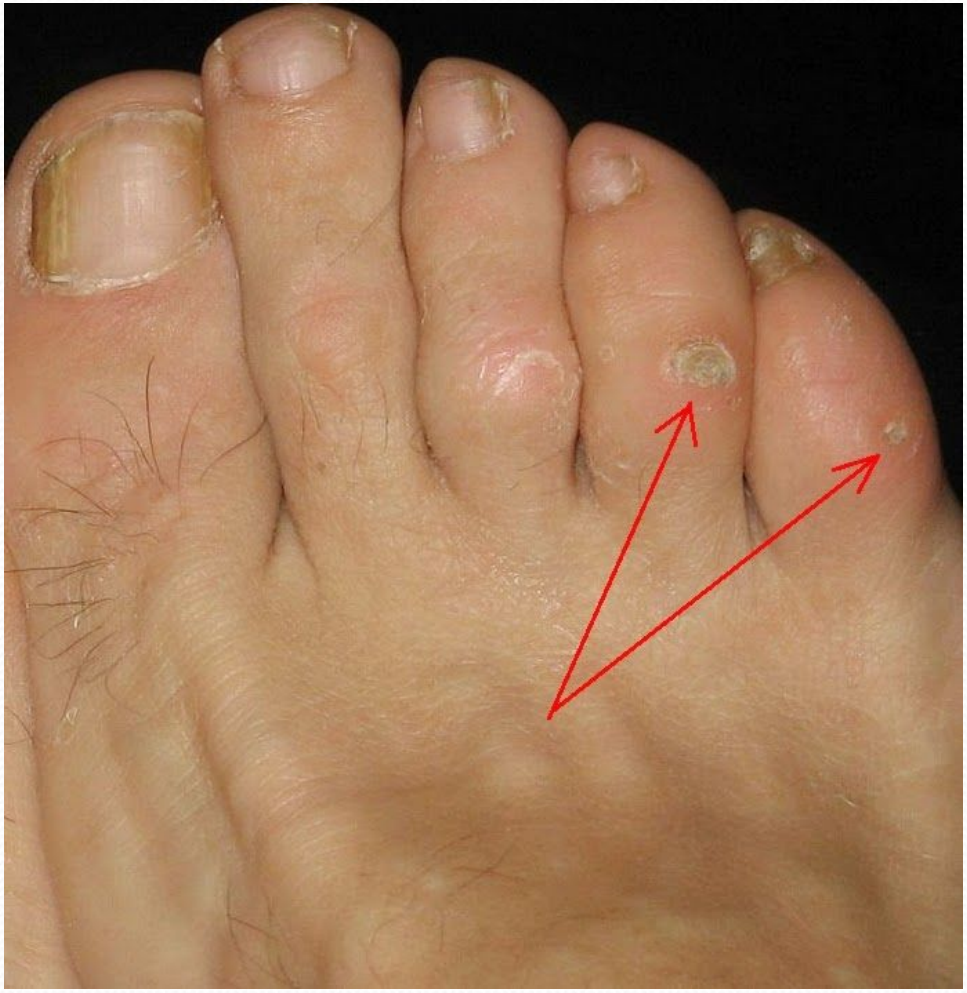
2-External application : salicylic acid is used topically to treat corn, calluses and epidermatophytosis. Like **Methylsalicylate**

3- Low dose aspirin(100mg) used **prophylactically** to decrease incidence of IHD.

4- Recurrent **abortion** (antiphospholipid syndrome).

Corn





Miscellaneous adverse effects and contraindications

- May decrease the glomerular filtration rate, particularly in patients with renal insufficiency.
- Occasionally produce mild hepatitis
- Prolong bleeding time.
- Aspirin irreversibly inhibits platelet COX-1 and COX-2 and, thereby, TXA2 production, suppressing platelet adhesion and aggregation.

- The use of salicylates is contraindicated in patients with bleeding disorders

- Salicylates are not recommended during pregnancy; they may induce:
  - postpartum hemorrhage
  - premature closure of the fetal ductus arteriosus.

In pregnancy: Aspirin cross placenta and it is classified as FDA pregnancy **category C risk** during **1st and 2nd** Trimesters and **category D** during **3rd Trimester .**

Because salicylates are excreted in **breast milk**, aspirin should be **avoided** during pregnancy and while **breast-fed**

- The use of aspirin and other salicylates to control fever during viral infections (influenza and chickenpox) in children and adolescents is associated with an increased incidence of Reye's syndrome, an illness characterized by vomiting, hepatic disturbances, and encephalopathy that has a 35% mortality rate.
- Acetaminophen is recommended as a substitute for children with fever of unknown etiology.

Side effects in over dose: on

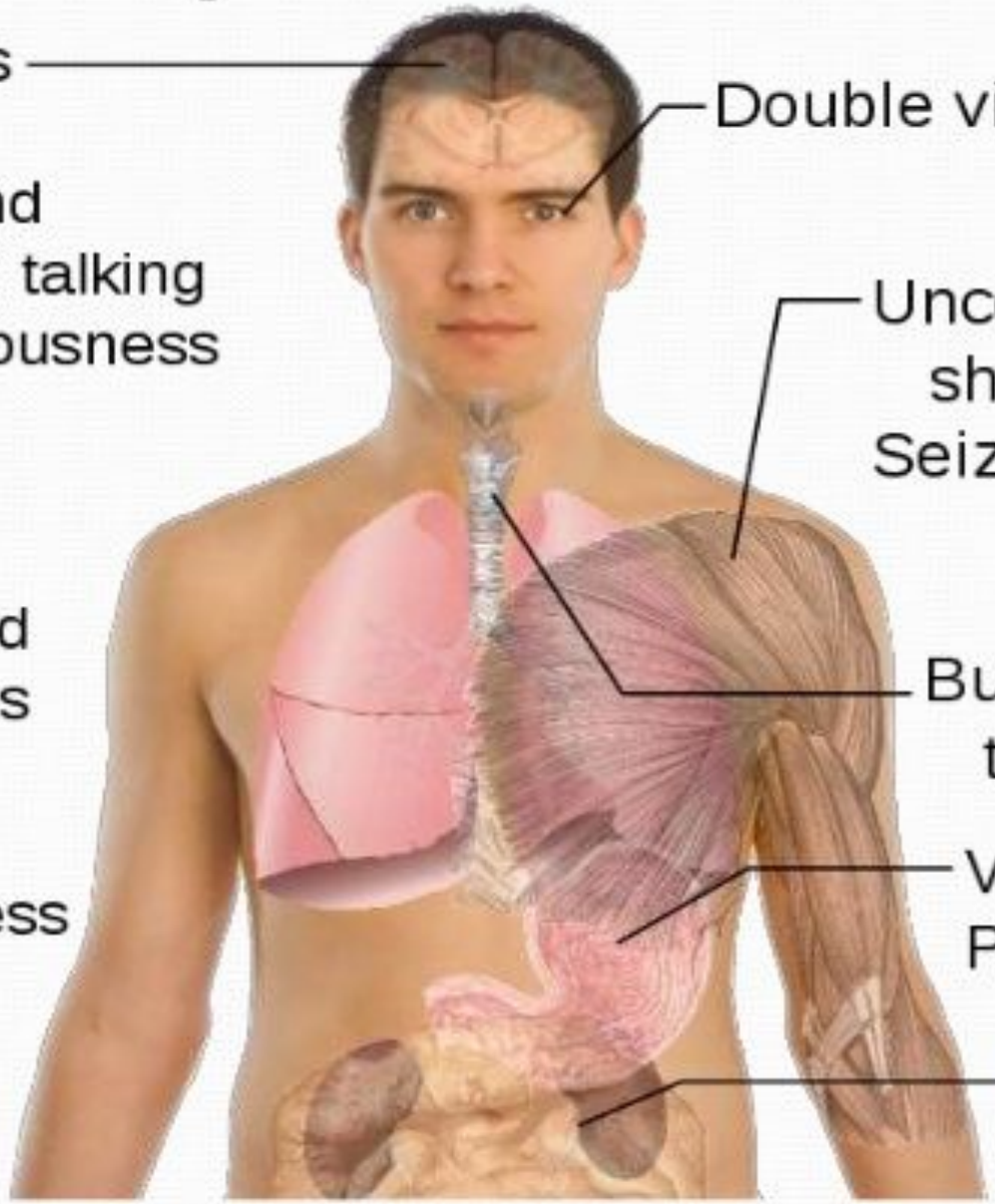
A- Respiration: In **toxic** doses, salicylates cause **respiratory depression** and a combination of **uncompensated** respiratory and metabolic **acidosis**.

B-Metabolic processes: **Large doses** of salicylates uncouple oxidative phosphorylation. The energy normally used for the **production** of adenosine triphosphate is dissipated as heat, which explains the **hyperthermia** caused by salicylates when taken in toxic quantities

C- Others: in the following picture.

Symptoms of

Aspirin overdose



Restlessness
Irritability
Excessive and unorganized talking
Fear or nervousness
Dizziness
Confusion
Abnormally excited mood
Hallucinations
Drowsiness
Loss of consciousness

Double vision

Uncontrollable shaking
Seizures

Burning throat pain

Vomiting
Pain

Systemic:
Fever

Decreased urination

2-Propionic acid derivatives : (ibuprofen, fenoprofen, naproxen, ketoprofen, flurbiprofen, oxaprozin).

They have advantage over aspirin , they are:

1-better tolerated at anti-inflammatory doses.

2-orally active

3-**oxaprozin** has long t1/2 and can administered **once** daily

4-undergo hepatic metabolism.

5- excreted via kidney.

6-Ibuprofen is **equal** to aspirin as **anti-inflammatory** effect but it is **more** effective **analgesic.**

7- should not be used in pregnancy.

3-Fenamates :(mefenamic acid and medofenamates):-

- Used as analgesics in rheumatoid arthritis and dysmenorrheal.
- Toxicity limits its use
- Have no advantage over other anti-inflammatory drugs.
- **Elderly** may develop renal failure due to dehydration.

4-Enolic acid derivatives: (piroxicam, tenoxicam, azapropazone) :-

- **Piroxicam** **equal** to aspirin and indomethacin in **anti-inflammatory** action
- **Long t1/2** (50 h) permit once daily dose.
- **GIT** side effects occur in **20%** of patients
- **Excreted** in **urine**.

5-Acetic acid derivatives: Ketorolac, Indomethacin , Nabumetone

They have anti-inflammatory effect with little analgesic and antipyretic effects.

Indomethacin is effective in

1- Pain associated with postoperative ophthalmological procedures

2- Antipyretic for Hodgkin's disease

3- Treating **PDA** (patent ductus arteriosus).

Contraindication:- pregnancy, nursing, patients with psychiatric disease, epilepsy, Parkinson, renal or GIT disease and machine operator.

Sulindac: similar to indomethacin with **half** its **potency** and **long duration** of action, given **orally** with **less side effects**.

Nabumetone :

-A pro drug absorbed from GIT after oral dose and converted in the liver in to active drug.

-t1/2 of 24 hr.

-It causes less gastric irritation.

Ketorolac

-Absorbed after oral and, completely after i.m injection,

-High protein binding, **60%** excreted **unchanged** in urine

-t 1/2 is 4-6 hr.

-Highly effective for postoperative pain(efficacy equal to morphine), topically used in allergic conjunctivitis, migrain.

6-Pyrazolone derivatives: Phenylbutazone, Oxyphenbutazone

Phenylbutazone is

- Powerful anti-inflammatory effect
- Weak analgesic and antipyretic effects
- Prolong t1/2 (50 hr)
- Has common and serious side effects.
- Used for short term treatment in acute gout (1week) and a rheumatoid arthritis when other drugs failed.
- Completely absorbed after **oral** dose
- Highly bound to plasma proteins.

B. Preferential COX-2 inhibitors: Nimesulide, Diclofenac, Aceclofenac, Meloxicam, Etodolac.

Diclofenac is a derivative of phenyl acetic acid

- rapid and complete oral absorption
- exposed to first pass metabolism.
- It is more potent than indomethacin and naproxen.
- **Preparations:** Oral, parenteral, skin, and ophthalmological
- it is accumulated in the synovial fluid.

Uses:- Rheumatoid arthritis, ……., postoperative pain, dysmenorrhea and renal colic.

Side effects:- **GIT** (in 20%) are the most common

-**Increase hepatic** enzymes.

-It is **not** indicated for **pregnant** or **nursing** mother and in **children**.

- **Nimesulide:**
- **Weak** inhibitor of **COX2**
- Act by **inhibition** of certain inflammatory mediators **TNF** alpha, matrix metalloprotenase.
- Completely absorbed
- 99% protein binding
- extensively metabolized
- Excreated in urine

C. Selective COX-2 inhibitors: Celecoxib, Etoricoxib, Parecoxib. rofecoxib :

COX-2 is present **more in inflammation** and COX-2 inhibitors have **less gastric** damage effects.

Celecoxib its effect is time dependant :

- **Irreversible**
- **not used** for **analgesia**
- **no** effect on **platelets** or blood
- given **once daily**.

The possibility that other COX-2 inhibitors may be associated with **increases risk** of thrombotic cardiovascular events **decreases** its **use**.

cardiovascular effects are most likely due to **inhibition** of COX-2 in **blood vessels**, which leads to a **decrease** in the production of **prostacyclin** in them.

Prostacyclin usually **prevents** **platelet aggregation** and **prevent** **vasoconstriction**, so its inhibition can lead to **excess clot** formation and **higher blood pressure**

D. Analgesic-antipyretics with poor anti-inflammatory action including

Acetaminophen :-

- is a Para-aminophenol derivative .

-It is an analgesic and antipyretic for adult and children.

-It acts by inhibiting PGs synthesis in CNS. It has less effect on COX in peripheral tissues.

-its analgesic efficacy is equal to that of aspirin but has only little anti-inflammatory effects

-Does not affect platelet function.

Used for mild and moderate pain such as headache, dysmenorrhea and fever when aspirin is contraindicated.

Kinetics:

- It is rapidly absorbed from GIT
- t1/2 = 2 hr.
- 3% excreted unchanged in urine
- most of the drug is conjugated with glucuronic acid in the liver and then excreted in urine.
- A portion of acetaminophen is hydroxylated to form **N-acetyl-benzoquinoneimine** (a highly reactive and potentially dangerous metabolite) which is in normal doses of acetaminophen reacts with sulfhydryl group of glutathione forming nontoxic substance

Side effects:-

A- at therapeutic doses; acetaminophen is well tolerated with less side effects include: skin rash, drug fever and decrease white cell count. Renal tubular necrosis is a **rare** side effect of prolonged use.

B- at **over doses**(10 g in adult and 4 g in child in one dose); can result in sever hepatotoxicity and doses over 20 g are fatal. The available glutathione in the liver become depleted and toxic metabolites of acetaminophen bind to liver cells producing hepatocellular damage occur 2-6 days after ingestion of the drug.

Treatment include:-

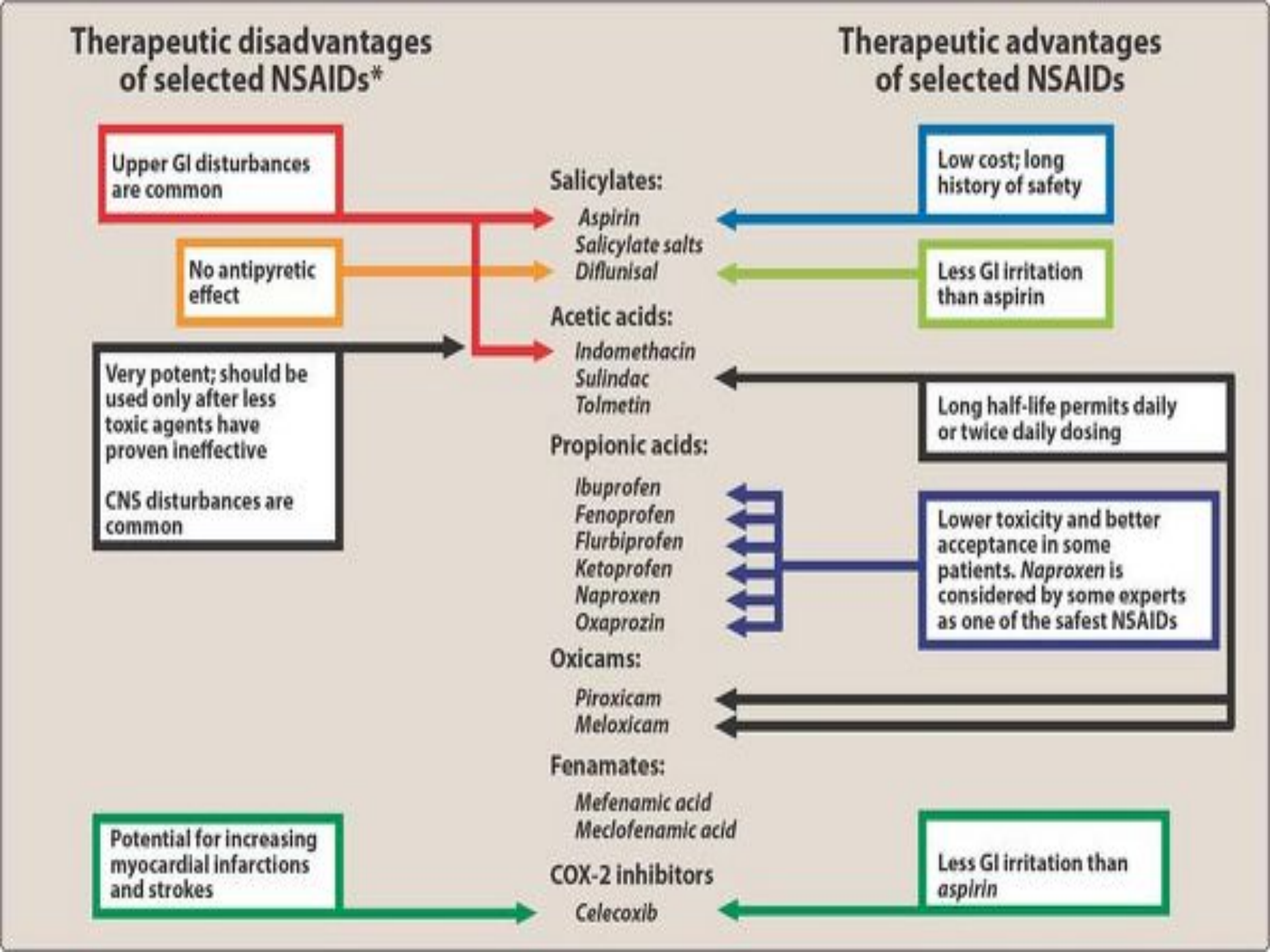
1- Empyting the stomach and administering activated charcoal.

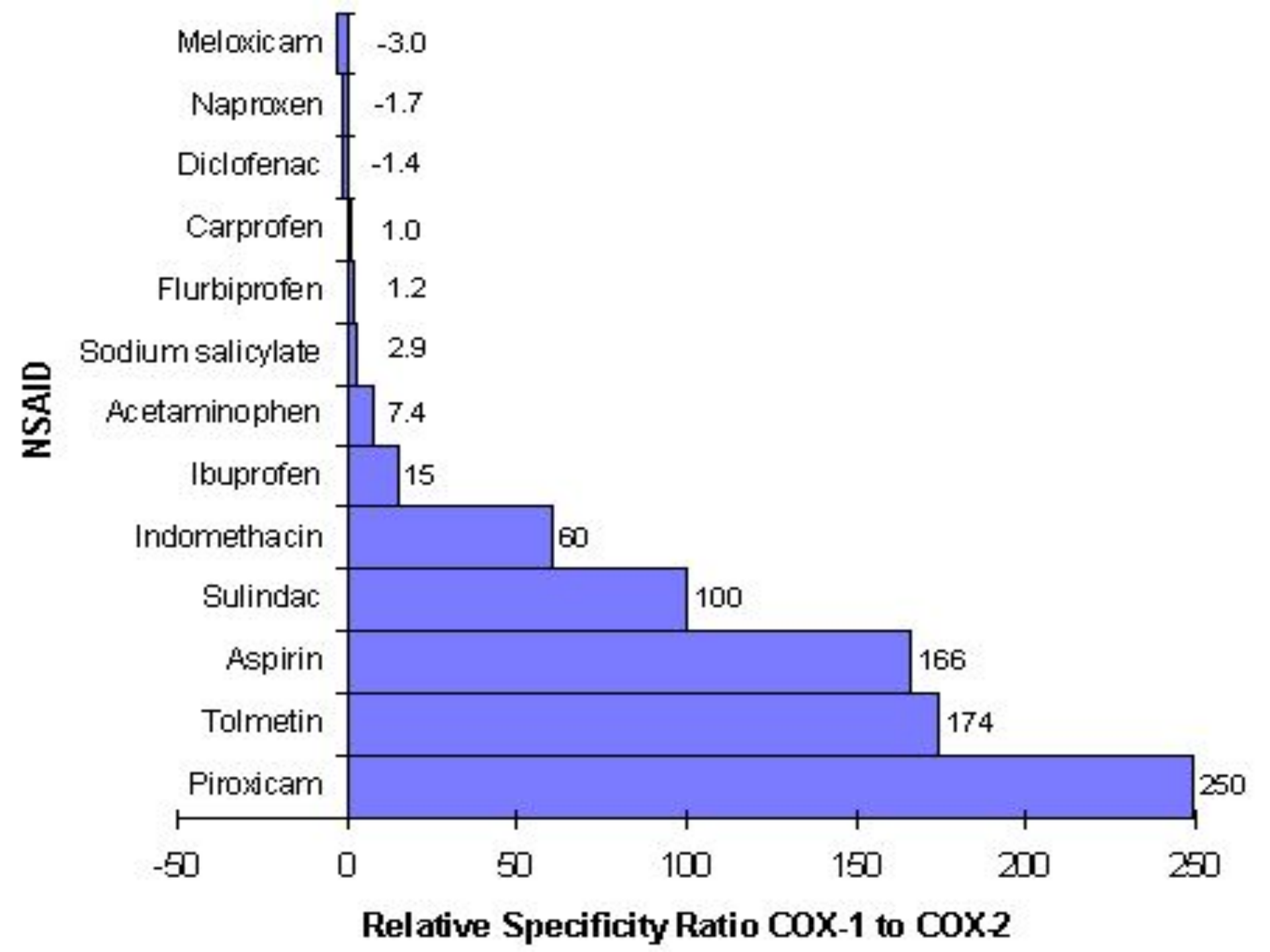
2- Hemodialysis within 12 hr. after ingestion.

3- Administration of **sulfhydryl compounds**

(**N-acetylcysteine** and **methionine** which are precursors for the synthesis of glutathione) **replenish** hepatic stores of glutathione. A paracetamol-methionine combination (pameton) have been used, the methionine content ensuring that hepatic glutathione concentration are maintained

when the drug is used in over dose.


Therapeutic disadvantages of selected NSAIDs*
Therapeutic advantages of selected NSAIDs
Upper GI disturbances are common
No antipyretic effect
Very potent; should be used only after less toxic agents have proven ineffective
CNS disturbances are common
Potential for increasing myocardial infarctions and strokes
Salicylates:
Aspirin
Salicylate salts
Diflunisal
Acetic acids:
Indomethacin
Sulindac
Tolmetin
Propionic acids:
Ibuprofen
Fenoprofen
Flurbiprofen
Ketoprofen
Naproxen
Oxaprozin
Oxicams:
Piroxicam
Meloxicam
Fenamates:
Mefenamic acid
Meclofenamic acid
COX-2 inhibitors
Celecoxib
Low cost; long history of safety
Less GI irritation than aspirin
Long half-life permits daily or twice daily dosing
Lower toxicity and better acceptance in some patients. Naproxen is considered by some experts as one of the safest NSAIDs
Less GI irritation than aspirin


Meloxicam
-3.0
Naproxen
-1.7
Diclofenac
-1.4
Carprofen
1.0
Flurbiprofen
1.2
Sodium salicylate
2.9
Acetaminophen
7.4
Ibuprofen
15
Indomethacin
60
Sulindac
100
Aspirin
166
Tolmetin
174
Piroxicam
250
NSAID
-50
0
50
100
150
200
250
Relative Specificity Ratio COX-1 to COX-2

Thank you