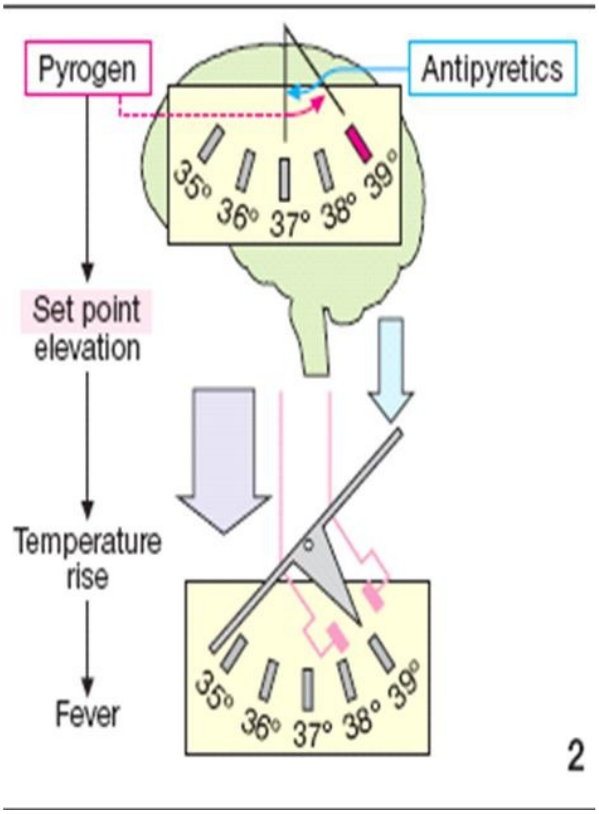
Non-steroidal anti-inflammatory drugs

THEY HAVE 3 PHARMACOLOGICAL ACTIONS:

- Antipyretic
- Analgesic
- Antiinflammatory

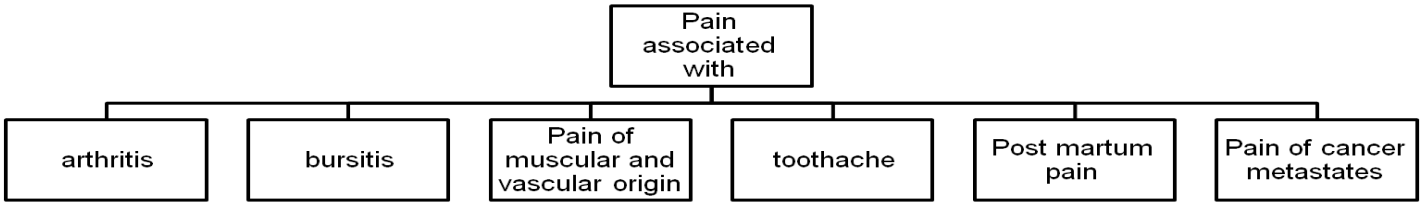


Antipyretic action:

- Fever raises the set temperature in hypothalamus
- NSAIDs decrease this set temperature
- Pyrogens released by macrophages (for example IL-1)
- These pyrogens will stimulate prostaglandin PG production in hypothalamus.
- PG raises the set point in hypothalamus —> fever
- NSAIDs inhibits production of PG
- NSAIDs have no action on normal temperature (37.2°)

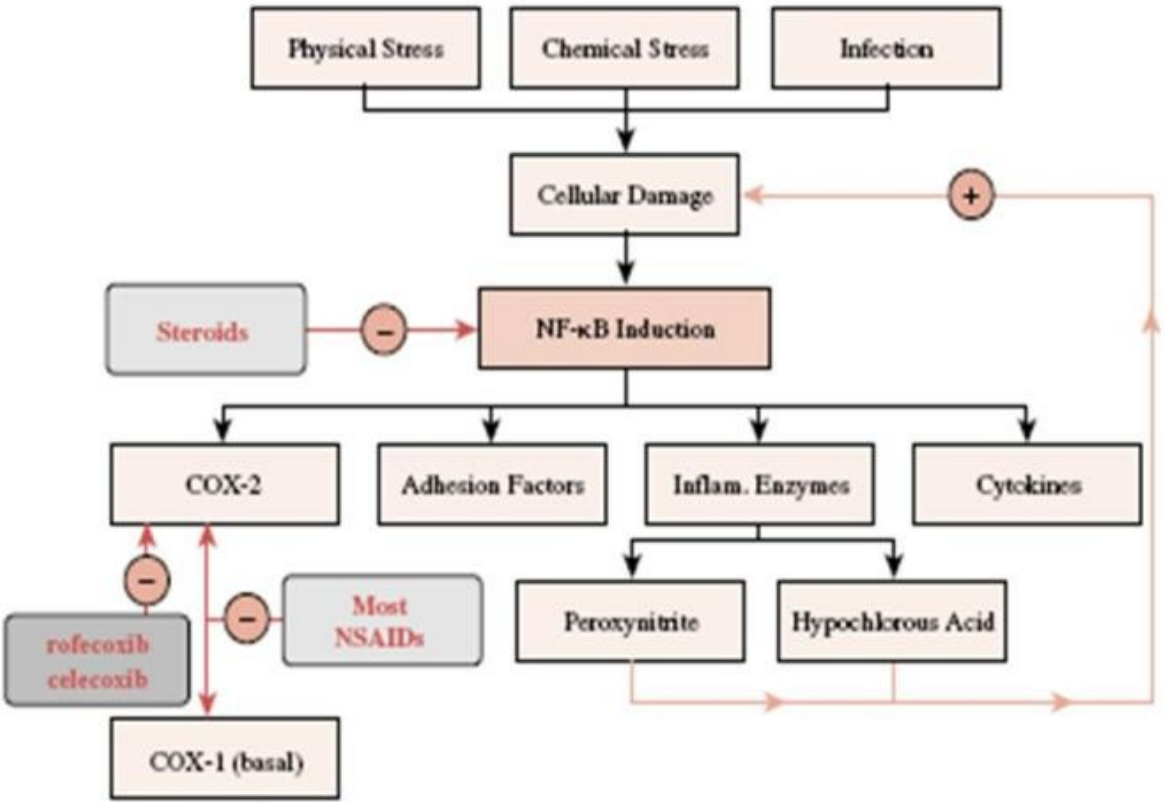
Analgesic action:

- They are effective in pain associated with inflammation.



Antiinflammatory action:

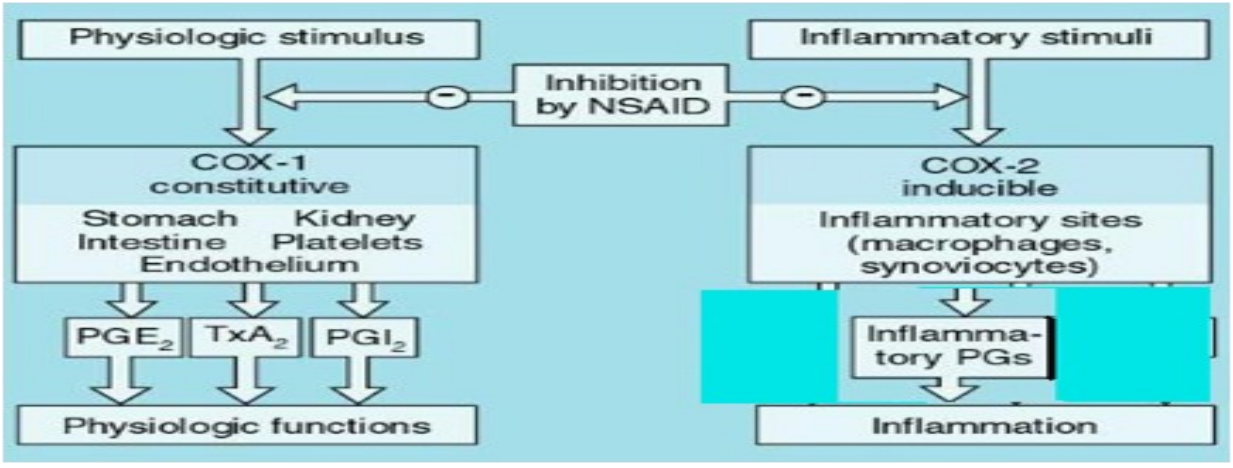
- They inhibits cyclooxygenase enzyme (COX) —> decrease production of PG
- They decrease production of oxygen radicals (ROS) —> ↓ tissue damage.
- They have no effects on lysosomal enzyme release.



MECHANISM OF ACTION:

3 types of COX enzyme:

- COX-1: constitutively expressed , widely distributed, maintains the normal physiological 'housekeeping' function.
- COX-2: inducible in inflammatory cells by inflammatory stimuli.
  - Expression is stimulated by growth factors, tumor promotersmers, cytokines, and endotoxins.
- COX-3: implicated in fever, expressed in the brain
- **Indomethacin & sulindac** primarily inhibit COX-1.
- **Meclofenamate & ibuprofen** have equally action on COX-1 &COX-2.
- Celecoxib & rofecoxib inhibit COX-2
- Drugs with short half-lives in the plasma remain in the joints for a long time and vice versa; long half-life acting drugs last longer in the plasma, and have a proportional level with that of the intrarticular concentration.
- COX-2 inhibitors have no effect on platelet function (thus no cardioprotctive properties), but of importance, have less effect on the GI system.
- NSAIDs decrease sensitivity of the vessels to bradykinin and histamine and reduce the incidence of colon cancer by about 50%.



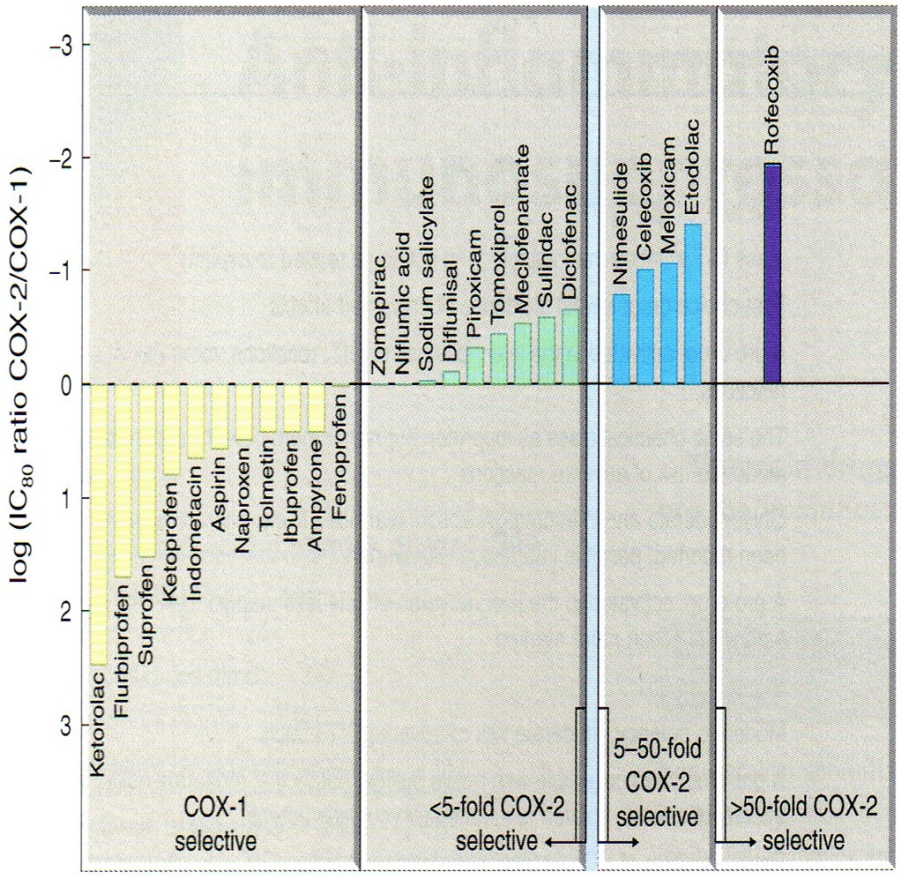


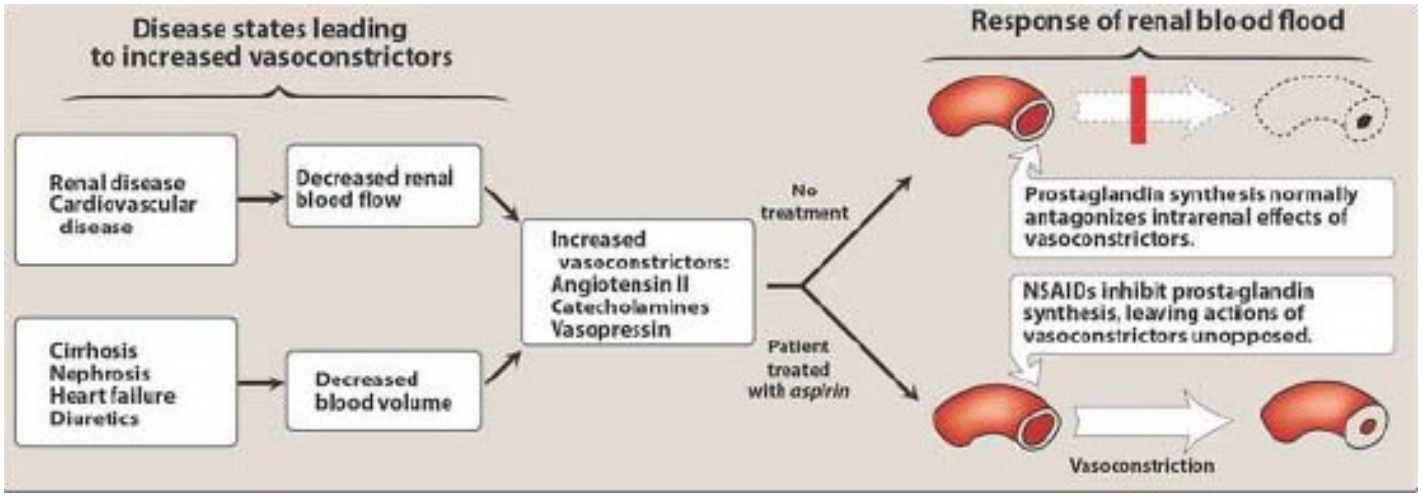
Fig. 16.1 A comparison of cyclooxygenase (COX) isozyme selectivity of non-steroidal anti-inflammatory drugs (NSAIDs). The graph shows the effect of various NSAIDs on COX-1 at a dose that gives an 80% inhibition of COX-2. The 0 line indicates equal potency. Those below the line have selectivity for COX-1. Some above the line have a less than fivefold selectivity to COX-2. The next group, containing meloxicam, etodolac, celecoxib and nimuselide, have a 50-fold selectivity towards COX-2; but note that all can produce full inhibition of COX-1. Only rofecoxib has a greater than 50-fold selectivity for COX-2. Activity measured in whole blood assay. (Modified from Warner et al. 1999 Proc Natl Acad USA 96: 7563–7568 as adapted by Vane 2000 Thorax 55: S3–S9.)

COMMON ADVERSE EFFECTS:

1. Gastrointestinal effects:

- result mainly from inhibition of the COX-1 isoform.
- dyspepsia, diarrhea, nausea, vomiting, gastric bleeding, and ulceration.

2. Adverse renal effects:



This figure illustrates the action of PG on the kidney

- NSAIDs inhibit the action of PG in the kidney thus impeding renal vascular auto-regulation.
- In susceptible pt. —> acute renal insufficiency.

3. Skin reactions (caused by **mefenamic acid** and **sulindac.**)

- Include: mild rash, urticaria, and photosensitivity reactions.

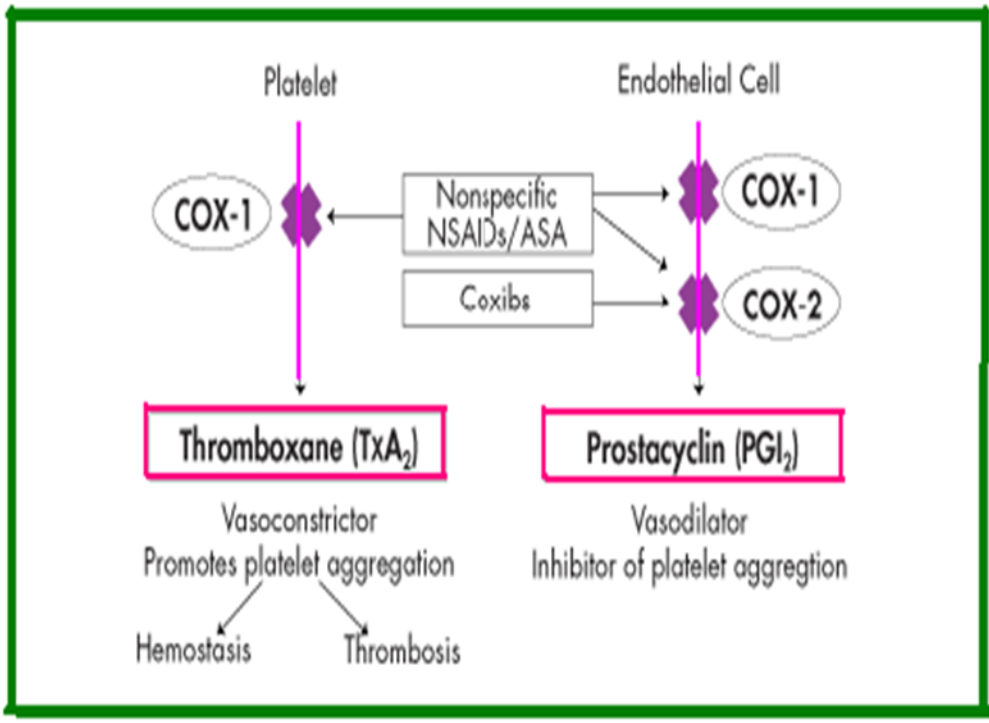
CLASSIFICATION OF NSAIDs

- Salicylates:- e.g. aspirin.
- p-Aminophenol e.g. paracetamol.
- Propionic acid e.g. ibuprofen
- Indole derivatives e.g. indomethacin
- Phenylacetic acid e.g. diclophenac
- Oxicam e.g. piroxicam, meloxicam.
- Fenamate:- Meclophenamic acid
- Naphthylacetic acid e.g. nabumetone

ANOTHER CLASSIFICATION OF NSAIDs

Nonselective COX inhibitors ← → **COX-2 selective inhibitors**

- COX-1 inhibition, in general, is instantaneous and competitively reversible.
- COX-2 inhibition is time dependent, i.e. its effect increases with time.
- The COX-2-selective drugs have minimal gastrointestinal toxicity.
- COX-2 inhibitors no impact on platelet aggregation.
- Cardiovascular thrombotic events seen in COX-2 inhibitors.
- COX-2 is constitutively active within the kidney.



SALICYLATES (ASPIRIN)

Mechanism of action:

- Non-selective Inhibitor of both COX isoforms
- Irreversibly inhibits COX and inhibit platelet aggregation

PK:

- Weak acid
- Most of it is protein bound
- $T_{1/2}$= low dose: 3h high dose: 15h
- Hydrolyzed by plasma and tissue esterases.

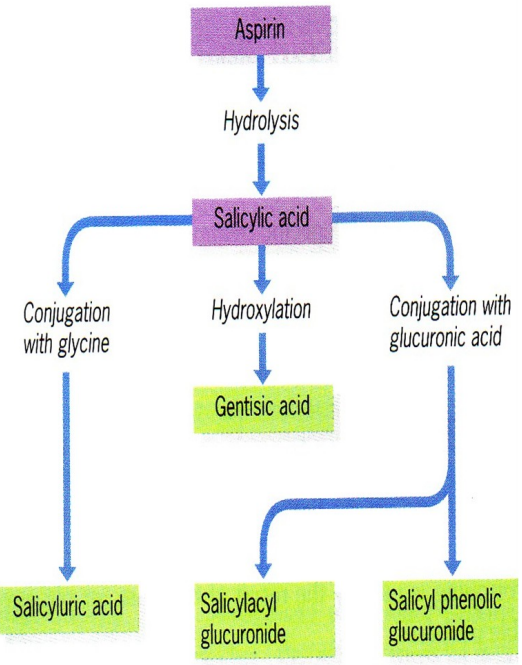


Fig. 16.9 The metabolism of aspirin.

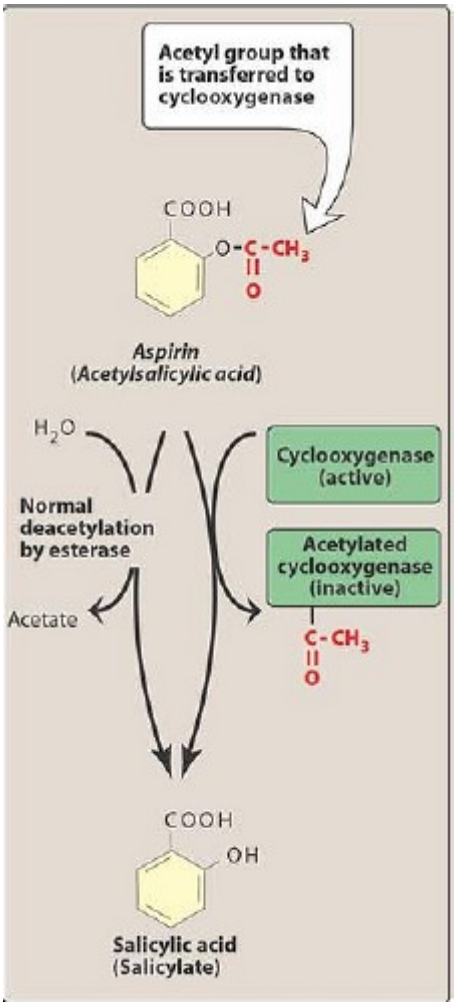
- **Metabolism:**

⇐ 25% oxidized

⇐ 25% excreted unchanged

⇐ some conjugated to glycine, glucuronic , & sulfuric acid

- Rate of excretion is higher in alkaline urine (Henderson-Hasselbalch equation).



Adverse effects:

- Contraindicated in hemophilic pt.
- GIT side effects: dyspepsia, nausea, vomiting, mucosal damage —> peptic ulcers.
- Analgesia-associated nephropathy
- Bronchospasm in aspirin-sensitive asthmatics
- Skin reactions
- Impaired homeostasis.
- Reye's syndrome: occurs in aspirin consumption by children with viral diseases such as chickenpox. (fatal disease)

Acute toxicity:

- Local effects:

Gastritis with focal erosion

- Systemic effects:

Salicylism: Large therapeutic doses alter acid-base balance —> hyperventilation & respiratory alkalosis.

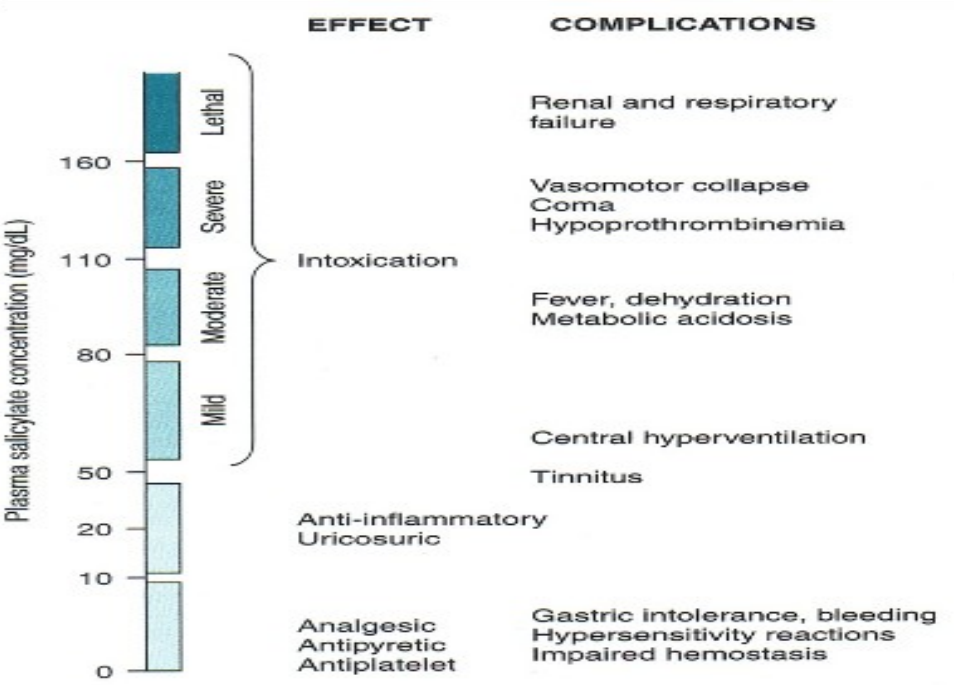
In larger doses —> respiratory acidosis.

Also Causes:

- Interference with carbohydrate metabolism —> metabolic acidosis
- Hyperpyrexia
- Dehydration
- CNS effects: initially stimulation with excitement then coma & respiratory depression.

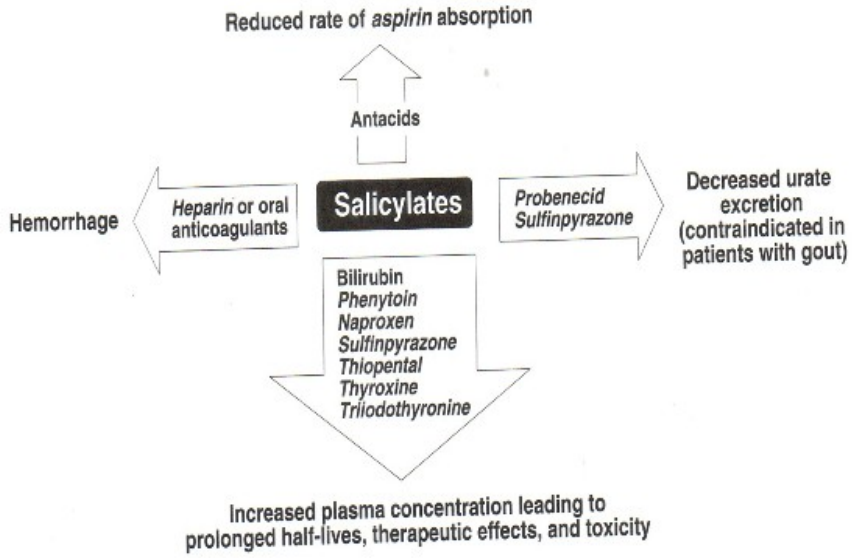
Treatment of toxicity:

- Correction of acid-base balance
- Rehydration and treat hyperthermia
- Maintenance of kidney function
- Gastric lavage & forced alkaline diuresis



Drug interaction:

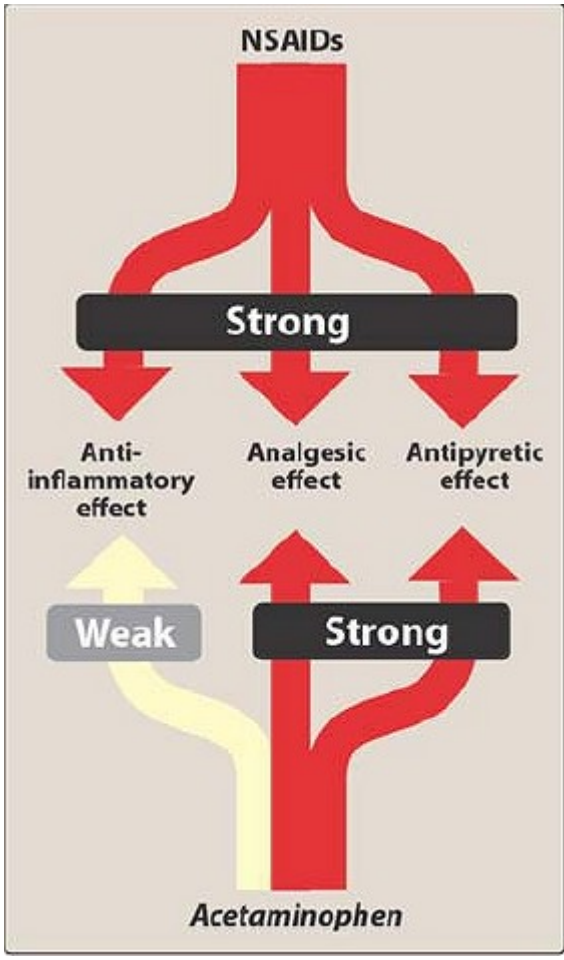
- Aspirin increases concentrations of: warfarin, phenytoin, valproic acid
- Avoid aspirin use with probencid & sulfinpyrazone because they increase uric acid excretion while aspirin does the opposite
- Ketorolac + aspirin = ↑ risk of GI bleeding and platelet inhi-bition



Clinical uses:

- Minor musculoskeletal disorders → bursitis, synovitis, tendinitis, myositis, and myalgia
- Fever and headache
- Inflammatory disease, such as acute rheumatic fever, rheumatoid arthritis, osteoarthritis, and certain rheumatoid variants, such as ankylosing spondylitis
- Prophylaxis of myocardial infarction and ischemic stroke.
- Colon cancer

PARACETAMOL (ACETAMINOPHEN)



Has no significant antiinflammatory effects and is usally used as an analgesic.

PK:

- Well absorbed orally
- Peak plasma concentration 30-60 m
- Variability in protein binding
- $T1_{/2}$= 2-4 h
- Drug is inactivated in the liver by conjugation with gluco
- uronic & sulfuric acid
- $T1_{/2}$ for toxic dose= 4-8 h

Adverse effects

- Allergic skin reactions
- Toxicity:

* The drug is metabolized to **N-acetyl-p- benzoquinone**.
* In normal doses the previous compound binds with glutathione, and is converted to mercaptopuric acid (nontoxic)
* With high doses **N-acetyl-p-benzoquinone** will cause <u>necrosis in the liver and kidney</u>
* Initial symptoms: nausea and vomiting
* Treatment:

1. Gastric lavage, oral activated charcoal.
2. Agents that ↑ glutathione formation e.g. **acetylsystine (orally or IV)**
3. Agents that ↑ conjugation reaction (**methionine & cystamine)**
4. After 12 hours these agents are useless and they may precipitate **hepatic coma**

Clinical uses

- Allergy to aspirin
- When slicylates are poorly tolerated
- Hemophilia
- History of peptic ulcer
- Bronchospasm precipitated by aspirin
- Children with certain viral infection
- Is usually combined with probencid

IBUPROFEN

A nonselective COX inhibitor

PK:

- $T_{1/2}$= 2 h
- Oral, cream preperation, and IV
- Hepatic metabolism and urinary excretion

Clinical uses:

- As an analgesic, antipyretic, in treatment of rheumatoid arthritis and degenerative joint disease.
- Closing patent ductus arteriosus in preterm infants
- A liquid gel preparation → postsurgical dental pain.
- Ibuprofen + aspirin = **no** platelet inhibition

Adverse effect

Nausea, heartburn, epigastric pain, rash, and dizziness, visual changes, prolongation of bleeding times

DICLOFENAC

Equal action on COX-1,2

PK

- Oral, IM, ophthalmic, topical,
- $T_{1/2}$= 1.1 h

Clinical uses

- Used for rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, dysmenorrhea.
- Topical for solar keratosis
- Usually combined with misoprostol or omeparazole to prevent upper GI bleeding
- Ophthalmic preparation → postoperative ophthalmic inflammation.
- Rectal suppository for preemptive analgesia and postoperative nausea

Adverse effects

- GI disturbances
- Headache
- Reversible elevation of serum transaminases.

PIROXICAM

Mechanism of action:

- Nonselective COX inhibitor
- In high concentrations it inhibits polymorphonuclear leukocyte migration, decreases oxygen radical production, and inhibits lymphocyte function.

PK

$T_{1/2}$= 57 h

Clinical uses:

Rheumatoid arthritis and osteoarthritis

Adverse effects:

GI reactions, edema, dizziness, headache, rash, and changes in hematological parameters.

MELOXICAM

Mechanism of action:

COX-2 selective inhibitor but less selective than celecoxib or rofecoxib for COX-2

Clinical uses:

Osteoarthritis, rheumatoid arthritis and certain acute conditions

Adverse effects

Low frequency GI effects

NABUMETONE

PK:

- The only nonacid NSAID
- $T_{1/2}$= 26 h
- A prodrug metabolized in the liver to 6-methoxy-2-naphthylacetic acid, a strong COX inhibitor, which is chemically similar to naproxen
- Renal impairment may double its t ½ .

Clinical uses

Rheumatoid arthritis, osteoarthritis, and pain management.

Adverse effects:

- Less damage to the stomach
- Pseudoporphyria and photosensitivity in some patients
- lower-bowel complaints, rashes, and CNS disturbances.

CELECOXIB

A COX-2 Selective inhibitor

PK:

- $T_{1/2}$= 11 h
- 27% urinary excretion

Clinical uses

Osteoarthritis and rheumatoid arthritis

Contraindications:

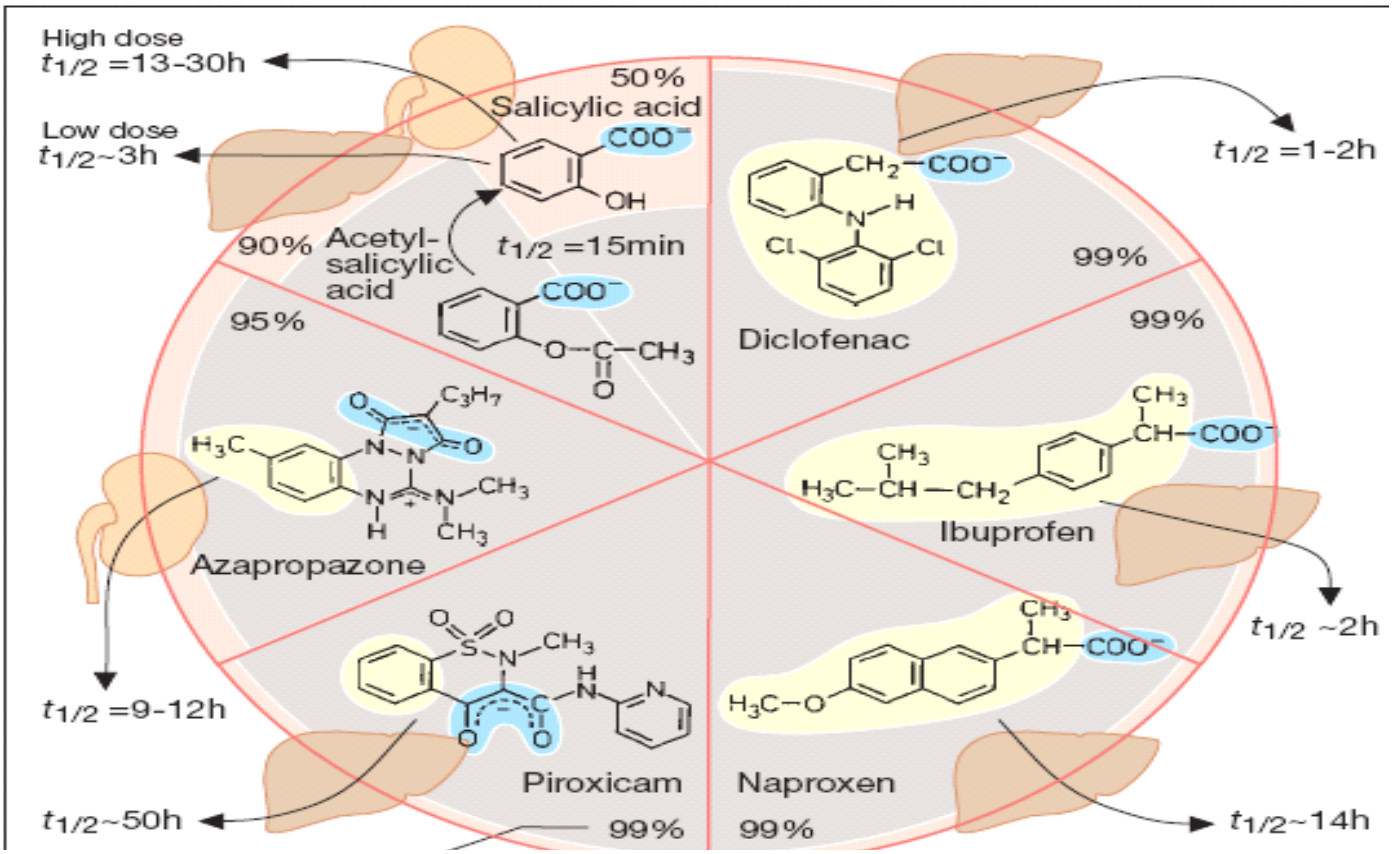
- Hypersensitivity to sulfonamides or other NSAIDs.
- Used with caution in persons with hepatic disease

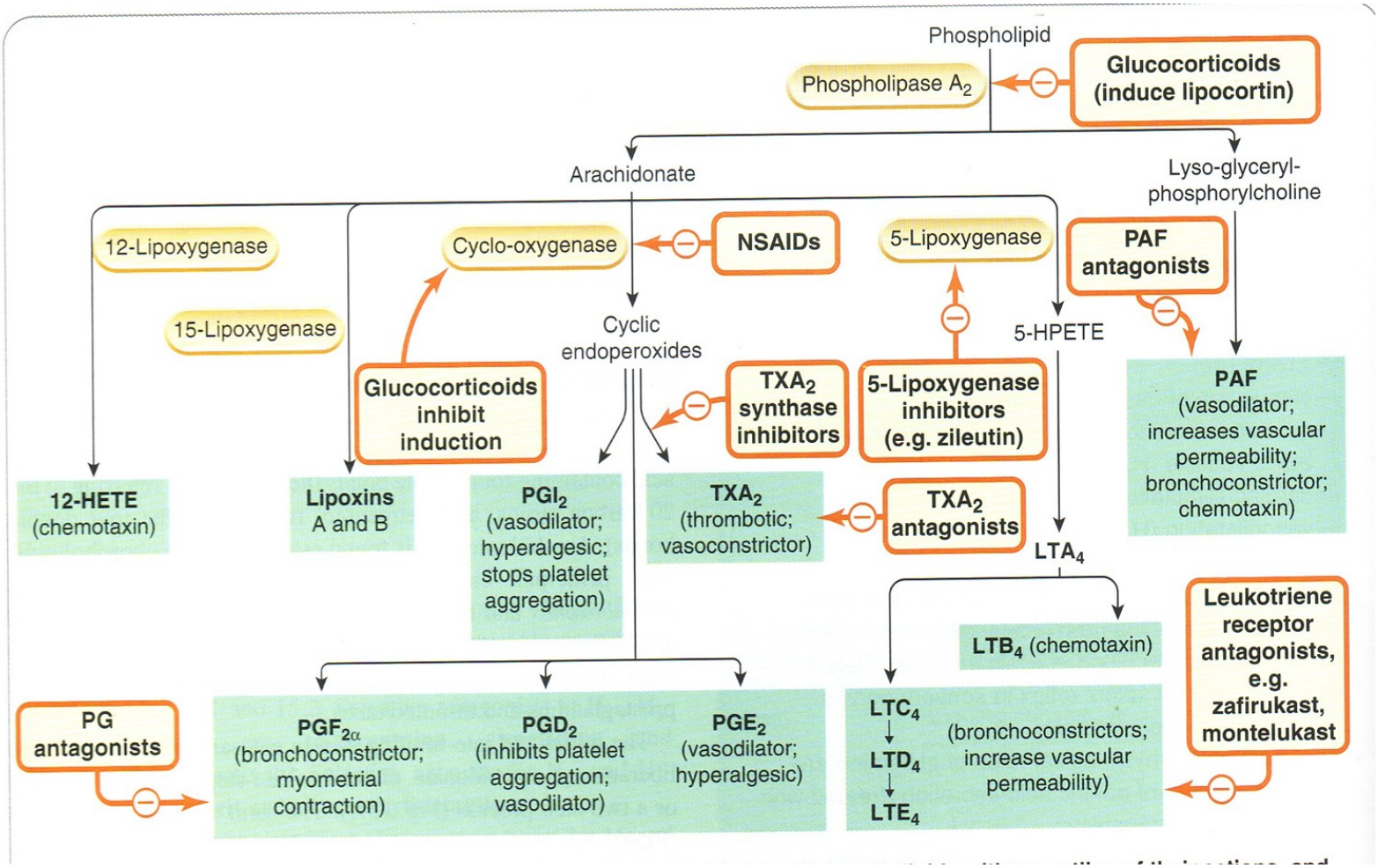
Drug interactions:

with other drugs that induce CYP2C9 (e.g rifampin) or compete for metabolism by this enzyme (e.g. warfarin, fluconazole, leflunomide).

Adverse effects:

- Mild to moderate GI effects such as dyspepsia, diarrhea, and abdominal pain.
- Serious GI and renal effects have occurred rarely
- hypertension and edema


High dose
$t_{1/2}$ =13-30h
Low dose
$t_{1/2}$~3h
50%
Salicylic acid
COO⁻
OH
90%
Acetyl-salicylic acid
$t_{1/2}$ =15min
COO⁻
O–C–CH₃
O
95%
$t_{1/2}$ =1-2h
CH₂–COO⁻
N
H
Cl
Cl
Diclofenac
99%
99%
C₃H₇
H₃C
N
N
O
N
CH₃
H
CH₃
Azapropazone
CH₃
CH–COO⁻
CH₃
H₃C–CH–CH₂
Ibuprofen
$t_{1/2}$ ~2h
$t_{1/2}$ =9-12h
O
O
S
N
CH₃
H
N
C
O
O
Piroxicam
99%
CH₃
CH–COO⁻
H₃C–O
Naproxen
99%
$t_{1/2}$~50h
$t_{1/2}$~14h


Phospholipid
Phospholipase A_2
Glucocorticoids (induce lipocortin)
Arachidonate
Lyso-glyceryl-phosphorylcholine
12-Lipoxygenase
Cyclo-oxygenase
NSAIDs
5-Lipoxygenase
PAF antagonists
15-Lipoxygenase
Cyclic endoperoxides
5-HPETE
Glucocorticoids inhibit induction
TXA_2 synthase inhibitors
5-Lipoxygenase inhibitors (e.g. zileutin)
PAF (vasodilator; increases vascular permeability; bronchoconstrictor; chemotaxin)
12-HETE (chemotaxin)
Lipoxins A and B
PGI_2 (vasodilator; hyperalgesic; stops platelet aggregation)
TXA_2 (thrombotic; vasoconstrictor)
TXA_2 antagonists
LTA_4
LTB_4 (chemotaxin)
Leukotriene receptor antagonists, e.g. zafirukast, montelukast
PG antagonists
$PGF_{2\alpha}$ (bronchoconstrictor; myometrial contraction)
PGD_2 (inhibits platelet aggregation; vasodilator)
PGE_2 (vasodilator; hyperalgesic)
LTC_4
LTD_4
LTE_4
(bronchoconstrictors; increase vascular permeability)