NSAIDS

COX ⊖

NSAIDS

Good: seen at Normal site

Cox-1

Constitutive.

(House keeping).

Also a bit seen at inflammation.

Cox-1 is produced normally at sites where they are required ie stomach etc.., It's normal one

Cox-2

Inducible.

- they are produced at Inflammatory site

Bad.

at Inflammation site But

- can also be at normal sites)

Kidney endothelium Brain

Normally Cox-2 occurs.

So we want to ⊖ COX 2. to ⊖ Inflammation. { we dont want to ⊖ cox-1 and jeopardise the normal function.

Cox-1

- ↑ PGs at normal site

Cox-2

- ↑ PGs at Inflammatory site

- not exclusive... both are seen at both actually

NSAIDS.

Non-selective Cox ⊖

Peptic ulcer ↑ { COX 1 also gets ⊖ }.

- fever ✓
- pain ✓
- Inflammation ✓

NSAIDS use.

Cox-2 ⊖

Peptic ulcer ↓ { only cox 2 ⊖ }.

* kidney damage ↑

Cox-1

- ↑ PGs at stomach

PGs → ↑ mucous, HCO3⁻

Cox-1 ⊖

↓ production ↓ peptic ulcer occurs.

All NSAIDS can be used in.

→ fever, pain, Inflammation.

Non-selective COX⊖

- paracetamol
- Aspirin
- Ibuprofen
- Diclofenac
- Indomethacin
- Ketorolac
- Piroxicam
- Nimesulide

→ we wanted to know, why there are many exceptions for paracetamol. then we found out

Exception → Paracetamol ⊖ COX-3 – which is only in CNS ✓ not in periphery

paracetamol → fever ✓ pain ✓ → can treat
paracetamol → inflam ✗ → not treated

peptic ulcer ✗ not seen.

kidney damage ↓ low. (DOC in kidney patients) C/I in liver pt.

paracetamol overdose.

- accidental overdose - children
- liver damage - (no glutathione)
- chronic alcoholics.
  - microsomal enzyme induction
  - not enough glutathione production.

Antidote → N-acetyl cysteine. = SH group ✓

kidney patients → paracetamol ✓

- paracetamol → ⊖ COX3

COX3 → Brain & spinal cord only. not in periphery.

so, fever ↓ pain ↓ but no anti-inflammatory action ✗ {inf occurs at periphery}

- Since no COX1 ⊖ → no peptic ulcer
- no COX2 ⊖ → no kidney problems.

→ actually, now some one saying COX⊖ is not major action, but it by to binding

paracetamol activates Vanilloid receptor.

Paracetamol poisoning

PCM → metabolism - microsomal.

NAPQI → – SH binds.

we were stopping for now

Continuation after few pages ✓

Cannot be given in liver damage.

alcoholics → microsomal enzyme induction → Liver damage ✓

Aspirin. Acetyl salicylic acid.

⇒ the only Irreversible Inhibitor.

due to irreversibility ↓ this also the only ⇒ Aspirin → antiplatelet

@ low dose (high dose no antiplatelet)

max dose - 325, above that → no antiplatelet action

⇒ Uric acid → won't be given in gout C/I

aspirin ↑ uric acid reabsorption

⇒ Children with viral infection C/I

Reye's syndrome.

⇒ poisoning → SALICYLISM.

OD of aspirin will ⊕ → respiratory centre ⊕

hyperventilation → ↓ CO_2 → respiratory ALKalosis

Mild poisoning symptoms

- respiratory alkalosis → Tinnitus. Headache. Blurred vision. vertigo.

@

- High dose poisoning occurs due to: { resp alkalosis will become metabolic acidosis } — occurs due to 3 reason,
  - Metabolic Acidosis →
    - HCO_3 excreted from kidney due to alkalosis
    - aspirin (acidic).
    - lactic acid (overwork of resp muscles).
  - ↓ Irreversible.
  - Severe dehydration → death

- There is no antidote for Aspirin

⇒ treatment? → Excrete Aspirin ✓.

$NaHCO_3$ → DOC

↓ makes Urine alkaline.

↓ aspirin (ionised)

↓ Excretion ✓

Ibuprofen

DOC in PDA

- Only approved anti-inflammatory in children
- (paracetamol - no anti inflammatory)
  { paracetamol is used in children, but not Anti inflamm }

Indomethacin

Causes

- Sedation.
- Headache → NSAIDs usually treat headache

Ketorolac

(& paracetamol) IV can be give IV, rest → IM

Piroxicam

longest acting NSAIDS. due to Enterohepatic circulation.

Nimesulide

Banned in children due to hepatotoxicity in children.

Non-Selectiv Cox ⊖ →	main problem: peptic ulcers.

So we made →

Selective Cox-2 ⊖

- Celecoxib. → peptic ulcer ✗, MI ✓
- Rofecoxib, Valdecoxib. } Banned. due to MI
- Etoricoxib

they are not preffered → they cause MI. ☆☆

- peptic ulcer is better than MI !

paracetamol poisoning {continuation}

paracetamol

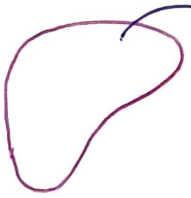
microsomal metabolism

NAPQI → high affinity for -SH group (sulphide group)

→ and this -SH group is seen everywhere. DNA, proteins, RNA etc..

- So, that means NAPQI is very toxic as it can bind to what all sites

→ But we know paracetamol is very safe... So how does this become safe?



Liver produces Glutathione

↓

it is a tripeptide, one AA among that is cysteine

↓

and it is sulphur containing.

ie, what all -SH NAPQI wants, Glutathione provides.

ie, normally

→ Normal paracetamol - NAPQI dose.

if say rto 100

→ Normally liver has, say 1000 Glutathione.

→ So normally it is not a problem as there is enough GT for NAPQI to bind.

problems can arise in the following case.

① Toxicity

- If high dose of paracetamol is taken

MC → in children

↓

due to strawberry flavoured paracetamol syrup.

② In liver damage

- not enough GSH to bind even for normal paracetamol dose.

③ Chronic alcoholism 😟

① alcohol is microsomal inducer

ie, even at normal doses of paracetamol high NAPQI concentration is seen

② In chronic alcoholic - there is liver disease. So not enough GSH

In alcoholics there is ↑ NAPQI & ↓ GSH. / Both

Antidote → N-acetyl cysteine

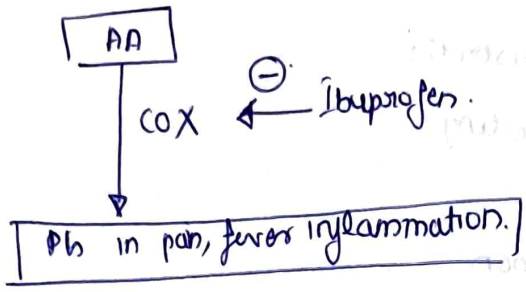
↓ ↑

NAPQI will bind to SH gp.

Q) Mechanism of Action & advantages of propionic acid derivatives.

Ibuprofen
Ketoprofen.
Naproxen.

PINK



- Non-selective COX Inhibitors ✓

advantages

1. Ibuprofen is available as OTC drug - used as a simple analgesic. especially effective in dysmenorrhoea.
2. Better GI tolerability than Aspirin
3. Safer for children in proper doses.
4. Does not cause Raye's syndrome. like aspirin.
5. Naproxen - most "cardio-friendly" NSAID

Selective COX-2 Inhibitors

Advantages

- Less GI Irritations : as they spare COX1. → fewer gastric ulcers & bleeding.
- Lower risk of affecting platelet function → minimal bleeding tendency.
- reduce pain, swelling, inflammation → good for arthritis, osteoarthritis, rheumatoid arthritis.

Disadvantage

- ↑ risk of heart attack, MI, stroke & thrombotic events.
- Kidney: Na, H_2O retention, edema.
- more expensive.

Aspirin ADR

① GIT - nauseo, vomiting.
epigastric pain, gastritis.
ulcerating, GI bleeding.

② Hypersensitivity - very common

② Reye's Sx - Viral infection in children (varicella/influenza) → hepatic damage with fatty infiltration. → encephalopathy.

① Analgesic Nephropathy.

③ high doses → produces "Salicylism" - dizziness, vertigo, Tinnitus.

① CCF precipitated in patients with low cardiac reserve.

④ Acute salicylate poisoning.

⑤ hemolytic anemia in G6PD deficiency.

CI

- Bleeding tendency
- peptic ulcer
- Chickenpox / influenza in children.
- HSR to aspirin.
- Chronic liver disease → It can ppt hepatic necrosis.
- G6PD deficiency → hemolytic anemia.

Table

DI

- NSAIDs - with glucocorticoids - potentiates GI complications
- ↓ efficacy of antihypertensives

In Text

- Aspirin displaces : warfarin, sulfonylurea, phenytoin, methotrexate. from binding sites. } overdose of these can occur.
- ↑ bleeding for patients on oral anticoagulants.
- Aspirin X probenecid → antagonise uricosuric effect of probenecid.
- aspirin blunts diuretic action of furosemide, thiazide, K+ sparing of spironolactone.

Guidelines in choice of NSAIDS

- Screenshot ✓

① mild pain/fever in kids → Ibuprofen.

② Chronic arthritis/osteoarthritis → Naproxen (Propionic acid)
Diclofenac (preferential)
COX-2 ⊖.

③ H/o ulcers/GI bleed → COX-2 ⊖.

④ CV risk → Naproxen ✓
avoid COX2 ⊖.

⑤ Kidney ds → avoid NSAIDS.

⑥ bleeding tendency → COX2 ⊖ preferred.

Difference

Aspirin	Celecoxib
• Non selective COX ⊖	• COX 2 ⊖.
• more GI SIE	• less GI SIE
• antiplatelet	• X
• No ↑ risk of clots, MI etc	• ↑ thrombotic events
• bleeding tendency	• X.