Paracetamol = Acetaminophen (USA)

- Antipyretic } Inhibit prostaglandin synthesis in the brain
- Analgesic }

- weak antiinflamatory effect } Less effect on cyclooxygenase inhibition in peripheral tissue.
- No effect on platelet function. or blood clotting time
- selective inhibitor of COX-3 cyclooxygenase enzyme?

pharmacokinetics:

Absorption: - administered orally
- well absorbed from GIT
- significant first pass effect
  - luminal cells of intestin
  - hepatocytes.

Metabolism: oxidation → Conjugated liver
cyt p450 glucuronidation → Non-toxic met.
↓ sulfoxidation
intermediate highly tox comp → N-acetyl benzoiminoquinone (highly toxic)
↓
hepatotoxicity.

excretion = urine

therapeutic uses:

- analgesic
- antipyretic

} ② particularly in patients complaining of gastric ulcer.

- prolongation of bleeding time
- No need for anti-inflammatory action

② in children with viral infection, Chickenpox

- Does not antagonize uricosuric agents
  - Probenecid
  - sulfinpyrazone
- Can be used in patients with gout.

Adverse effects:

therapeutic dose = No or few side effects

e.g. allergic skin reactions } transient
change in leukocyte count }

large dose = regular over long period of time

symptoms: Nausea vomiting → Risk of kidney damage → Renal tubular necrosis
- hypoglycemic coma

acute
Toxic dose = attempted suicide, accidental child intoxication

2-3 times therapeutic dose

② acute hepatic Necrosis → fatal ② renal necrosis
& N-acetylbenzoiminoquinone (intermediate toxic compound) (oxidation Cyt p450) accumulate in hepatocytes due to depletion of available glutathione in the liver → reacts with by covalent bonds with sulfhydryl groups of hepatocytes → hepatocytes necrosis, death

Tx: = gastric lavage + activated charcoal + acetylcysteine

Propionic acid derivatives:

- Ibuprofen
- Naproxen
- Fenoprofen
- flubiprofen
- keto prophen
- oxaprozin

Effect

- anti-inflamatory
- analgesic
- antipyretic
- antiplatelet

Toxicity

- Low toxicity.
- better acceptance in chronic use of RA
- GIT toxicity Less than aspirin
- reversible inhibitors of cyclooxygenase

Naproxen = Safest

pharmacokinetics

absorption: well absorbed after oral administration
distribution: totally bound to plasma protein
metabolism: hepatic metabolism → excreted in urine
half-life: oxaprozin = longest $T_{\frac{1}{2}}$, administered once daily.

Side effects: GIT = dyspepsia → bleeding
CNS = headache
tinnitus
dizziness

Acetic acid derivatives:

- Indomethacin
- Sulindac
- Tolmetin
- etodolac

action

- anti-inflamatory very potent.
- analgesic
- antipyretic

therapeutic use

- only after less toxic agents have proven ineffective
- toxicity limits its use
- Not used as antipyretics & gouty attacks.
- used in ankylosing spondylitis & osteoarthritis of hip

Side effects

- GIT
- CNS - common
- Cardiac

Sulindac

prodrug
long $T_{\frac{1}{2}}$ - once or twice daily.

oxicams

- Piroxicam } ++ in RA =
- Meloxicam }
  - ankylosing spondylitis
  - osteoarthritis

- long half-life = once daily
- renal ~~elimination~~ elimination & metabolism

side effects = GIT

inhibit both COX-1 & COX-2

fenamates = Mefenamic acid
Meclofenamic acid

* anti-inflamatory
* side effects - diarrhea - can be severe
  - bowel inflamation
  - haemolytic anaemia

Celecoxib - COX-2 inhibitors

(5)

Mechanism of action:
- More selective inhibitor of COX-2 than COX-1
  - time dependable & reversible.
  - No effect on platelet aggrigation.

uses: - RA
- osteoarthritis
- pain
- pt's with gastric ulcer.

kinetics:
- well absorbed from GIT
- extensively metabolized in liver by Cyt-p450 system
- excreated met. in urine & faeces.
- $T_{1/2}$ about 11 hours.

adverse effect: Headache
dyspepsia
diarrhoea
abdominal pain
allergy - sulfonamide allergy

avoid in: kidney toxicity → avoid in chronic renal insufficiency.
- severe heart disease
- dehydration
- hepatic failure

drug interaction: β-blockers
antidepressants
antipsychotics.

of Gout

- Metabolic disease.
- High uric acid in blood. ↑ production / ↓ excretion
- ppt of sodium urate crystals in tissues specially joints
- arthritis = due to deposition in synovial membranes
  - inflamation
    - kinin secretion
    - leukotrienes B4
    - accumulation of neutrophils
    - tissue damage
    - etc.

Drugs used to treat gout:

- allopurinol → inhibit uric acid synthesis
- probenecid & sulfinpyrazone → uricosuric agents → ↑ uric acid secretion
- colchicine → inhibit leucocyte migration into the joint.
- NSAIDs → - antiinflamatory
  - analgesics

Allopurinol

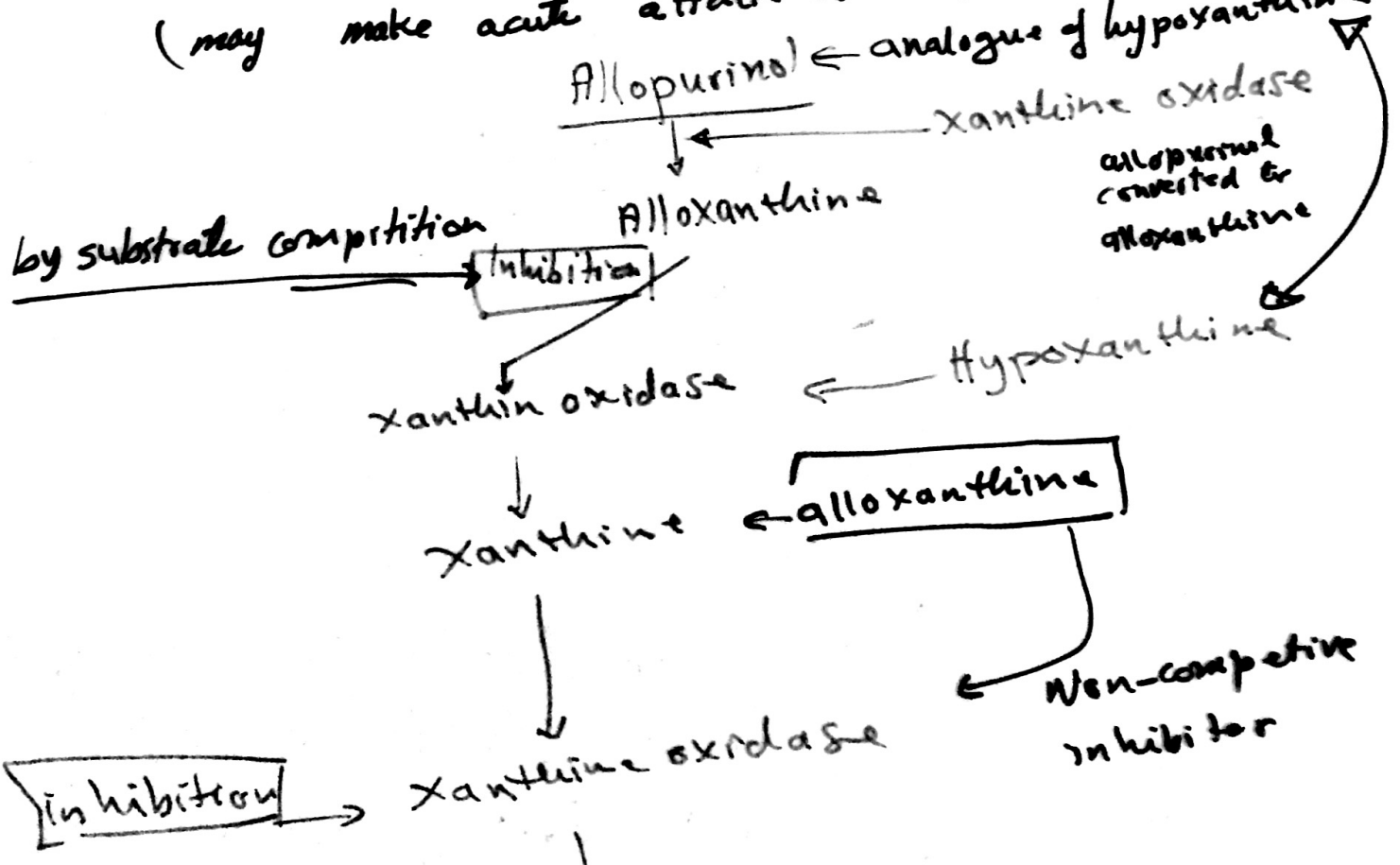
Mechanism of action

inhibit xanthine oxidase enzyme → ↓ of synthesis of uric acid.

→ reduce urate crystals deposition in tissues

– reduces formation of urate renal stones

- Drug of choice in Chronic treatment of gout (Long term ttt)
- Not effective in treatment of acute attack (may make acute attack worse)



Kinetics

- orally
- well absorbed
- $T_{1/2}$ = 2-3 hours
- Metabolism → xanthine oxidase → alloxanthine $t_{1/2}$ 18-30hrs
- Renal excretion → urine.

Colchicine

- used in acute attacks.
  - prevention
  - + treatment

act on neutrophils.

Kinetics

- orally
- well absorbed
- excreated mainly in GIT partly by urine

unwanted effects

GIT = mainly

- Nausea
- vomiting
- abdominal pain
- diarrhea
- haemorrhage
- kidney damage
- Rashes
- peripheral Neuropathy
- blood dyscrasias.