Nonsteroidal Anti – inflammatory Drugs

Nonsteroidal Anti- Inflammatory Drugs

Non – narcotic / Non –opioid analgesics

- **Pain – Two components**

(i) Peripheral component – Nociceptive afferent neurons stimulated by noxious stimuli

(ii) Central component – Afferent inputs generate a pain sensation

Two types

Integumental pain

Visceral pain

NSAIDS

1. **Not a steroid**
2. **Analgesic, Antipyretic, Anti-inflammatory**
3. **No CNS, RS depression**
4. **No Drug dependence**
5. **Act by inhibiting cyclo-oxygenase enzyme decrease in PG Synthesis**

Classification of NSAIDS

1 Nonselective **irreversible** inhibitor of cox
Aspirin

2. Nonselective **reversible** inhibitor **of cox**
Ibuprofen, Flubriprofen, Indomethacin, Mefenamic acid, Piroxicam, Ketorolac

3. **Preferential** Cox-2 Inhibitors
Nimesulide, Meloxicam, Diclofenac, Acelofenac

4. **Selective** Cox-2 inhibitors
Etoricoxib, Celecoxib, Parecoxib

5.cox3 inhibitor
Paracetamol

Cyclo-oxygenase enzyme

- COX1-Constitutive form
- COX2-Inducible

Mechanism of action

Tissue injury ⟺ PG release ⟹

1) mediators of inflammation, sensitize pain receptors at nerve endings.

2) Potentate action of other mediators at pain receptors – 5 HT, histamine, bradykinin ,TNFalfa ,IL .

NSAIDS-Inhibit COX ENZYME.

Inhibit synthesis of PGs from arachidonic acid

- ***Aspirin***

  Actions and Uses

- Oldest NSAID
- Converted in body to Salicylic acid

1 Analgesia

- Irreversible inhibitor of cox1, cox2 by acetylation of cox enzyme.

- Return of cox activity depends on synthesis of fresh enzyme

- PG synthesis

  ↓

- Action of other inflammatory mediators

  ↓

Use – 600 mg QID

Headache, Backache, Migraine, Toothache, Myalgia, Dysmenorrhea

2. Antipyretic action

Fever d/t infection or inflammation-

- Bacterial endotoxins release IL1,TNFAlpha from macrophages-stimulates PGE_2 generation -↑ temp.
- Inhibit COX1, 2 - ↓ PG synthesis in hypothalamus -reset the hypothalamic thermostat.
- Aspirin doesn't inhibit heat production
- Increase heat loss-peripheral vasodilatation and sweating

Use- Treatment of fever of any origin

2.Anti – inflammatory effect

1 Cox- 2 - PGs → vasodilatation, oedema

2. Stabilizes leukocyte, lysosomal membrane

3. Leucocyte infiltration

4. Quenching of free radicals

Use – Dose -75-100 mg/kg/ day

Osteoarthritis

Rheumatoid arthritis

Rheumatic fever

3.Inhibition of platelet aggregation

-Irreversibly inhibits Cox-1 of platelets

-Acetylates Cox-1 of platelets in portal circulation before aspirin is deacetylated in liver

Small dose is sufficient as antithrombotic

- The enzyme is inhibited for life-time of platelets
- Decrease TXA2 production

Use –

1 Primary and secondary prevention of MI

2.Stroke

3.TIA

Low –Dose -75-325 mg/day

4.Relief of Dysmenorrhea

- level of $PGF_2\alpha$ -- uterine contraction – Uterine ischemia – uterine cramps
- Normalizes excess flow

Use – Dysmenorrhea

5.Closure of Ductus Arteriosus

Kept patent in fetal life by PGE_2, I_2

- Synthesis switched off at birth- ductus closes
- Small dose aspirin , endomethacin

Salicylic acid- Topical –keratolytic

Adverse effects

Gastric mucosal damage

1. Inhibition of cox 1 ↓ PG synthesis ↓ gastro-protective effect of PGs

   S/E – dyspepsia, gastric Ulceration, gastric bleeding

2. Back diffusion of H+ ions
3. ↓ Secretions of HCO3-
4. Local back diffusion of acid- focal necrosis of mucosal cells and capillaries

Mainly with anti-inflammatory dose

Less with selective cox-2 inhibitors

-**Increase in bleeding tendency**

- prolongs bleeding time

-Aspirin to be stopped one week before surgery

Precipitate bronchial asthma

Inhibition of cox – diversion of arachidonic acid to 5-Lipoxyagenase pathway --- formation of leukotrienes

Renal Effects

- ↓ uric acid excretion –by ↑ uric acid secretion
- Impairment of renal bld flow
- COX2 dependent inhibition of Na+ and water retention
- Papillary necrosis

- **Reye's syndrome**
  - Rare
  - Aspirin given to children suffering form febrile viral infection
  - Liver damage, encephalopathy

Aspirin taken at term

delays onset of labour

Premature closure of ductus arteriosus

Drug interactions

with warfarin ,probencid ,sufonyl ureas

with methotrexate

- **Non – selective reversible**

Propionic acid derivatives

Ibuprofen

Safest NSAID

Weak anti-inflammatory

Not suitable for acute conditions

400 mg TDS

Flurbiprofen

Eye – drops, gel

Naproxen

More efficacious as anti-inflammatory

better tolerated

Effectivesly inhibit Leucocytes

Use - osteoarthritis ,R.arthritis, gout

Dose-250 mg BD

Fenamates

Mephenamic **acid**

Analgesic, Antipyretic

Weak anti inflammatory

Use - Dysmenorrhea- 250mg -500mg TDS

S/E- Diarrhoea

Enolic acid derivatives

Piroxicam

- Lowers PG concentration in synovial fluid

-Decreases production of IgM rheumatoid factor

- Long acting.

-GIT S/E more common

Use – OA ,RA ,gout ,dentistry

- 20 mg OD

Acetic acid derivatives

Ketorolac analgesia = opioid

post operative pain

Musculoskeletal pain

Oral-10-20mg QID, parenteral

Indomethacin

- More potent than Aspirin
- More GIT upset ,Pancreatitis,
- CNS S/E-Headache, confusion, dizziness
- Reserve drug
- Ankylosing spondylitis, RA, Fever refractory to other antipyretics -25mg BD
- Most common drug used for Closure of PDA
- Eye drops, Mouth rinse-gingival inflammation

- Nabumetone

-Forms active metabolite

-Lower incidence of gastric irritation

500-1000 mg/day

Preferential COX-2 Inhibitors

Diclofenac sodium

-Most extensively used NSAID

- High concentration in synovial fluid, good tissue penetrability

-Gastric ulceration –less common ,more hepatotoxic and renotoxic

- 50 mg TDS, eye-drops, gel, inj
- use --RA ,OA, ankylosing spondylitis ,renal colic ,dysmenorrhea

Acelofenac

-Enhancement of glycosoaminoglycan synthesis-chondroprotective property

-Long acting-100mg BD

Meloxicam

-less toxic than piroxicam

Nimesulide

-Sulfonamide compound

-Weak inhibitor of PG synthesis

- Reduced superoxide generation
- Free radical scavenging action
- Inhibition of PAF synthesis
- Withdrawn from some countries- Hepatic failure

-Preferred in asthmatics, Intolerant to other NSAIDs

Selective Cox-2 inhibitors

- Called coxibs
- Less GIT side effects
- Rofecoxib, Valdecoxib – Withdrawn from market - Increase CVS, cerebro-vascular risk

Reduce whole body PGI_2 production without affecting TXA_2 contents in platelets(COX-2 absent in platelets)-prothrombotic effect

- Celecoxib-100-200 mg BD, Etoricoxib-60-90mg OD
- Preferred in patients –at risk of peptic ulcer, perforation d.t.low ulcerogenic potencial

Paracetamol

Analgesics

Antipyretic

- Very less anti –inflammatory action-Inability to inhibit COX in presence of peroxides at inflammatory sites
- **Cox -3 New cox isoenzyme**

  Abundant in cerebral cortex

  Involved in pain perception, fever, not in inflammation
- **Paracetamol – Selective cox- 3 inhibitor**
- **No gastric mucosal damage ,no stimulation of respiration, no platelet action**

- **Toxic dose of paracetamol**

Hepatotoxicity – N acetyl- P Benzoquinoneimine

- Paracetamol metabolized by glucoronide conjugation. Small amount of toxic metabolite is formed by cytochrome P- 450 enzymatic system . It gets detoxified by glutathione conjugation.

  Toxic dose- large amount of toxic metabolite is formed – Can't detoxified through glutathione conjugation.
- Form covalent bond with hepatic proteins
- Necrosis cell death

Treatment

N- acetyl cysteine – has SH group like glutathione – Replenish stores of glutathione and themselves conjugate with toxic metabolite.

150mg/kg I v infusion in 200ml of 5%dextrose over 15 mins., repeated for next 20 hrs.

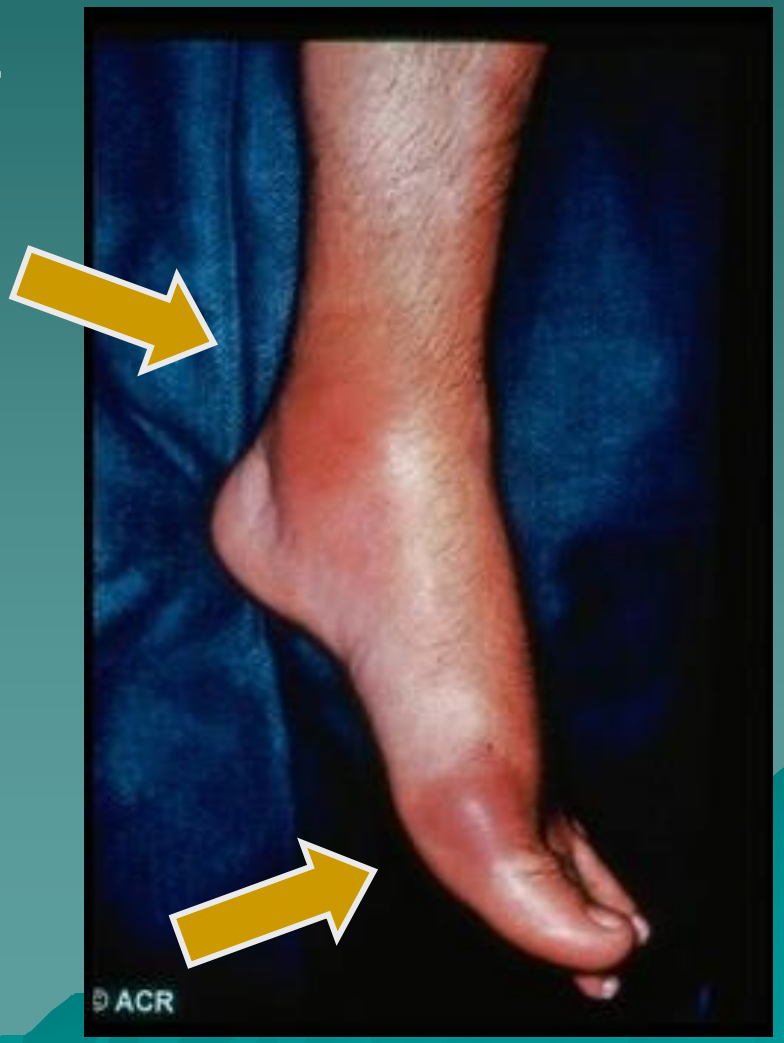
- CI- Premature infants-risk of hepatotoxicity
- Use---common OTC drug
- Best Antipyretic, Analgesic

- **Choice of NSAIDS**
- **Combinations-additive**

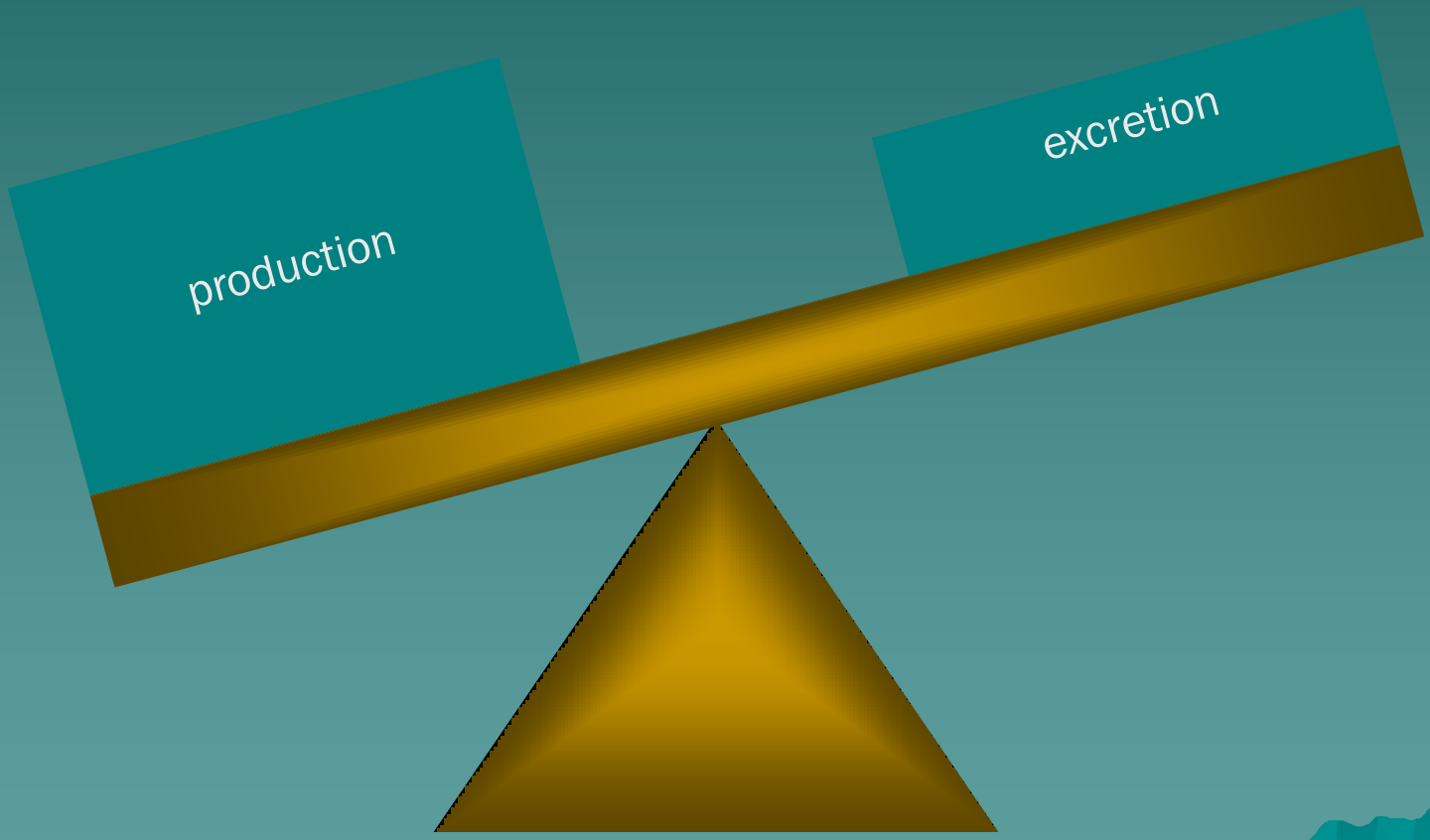
Gout - acute arthritis

acute synovitis, ankle & first MTP joints

Localized deposit of monosodium urate crystals

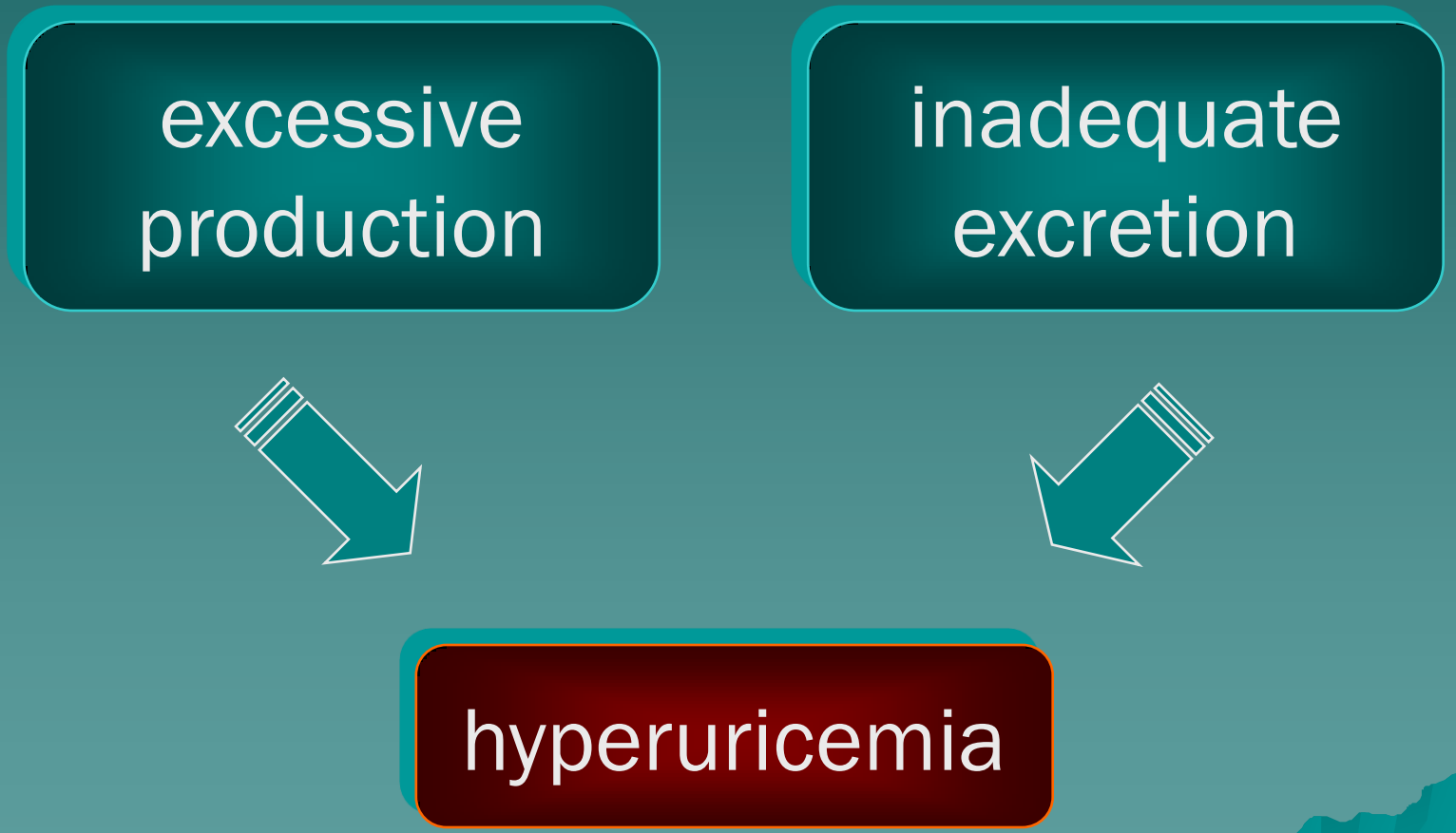


Hyperuricemia

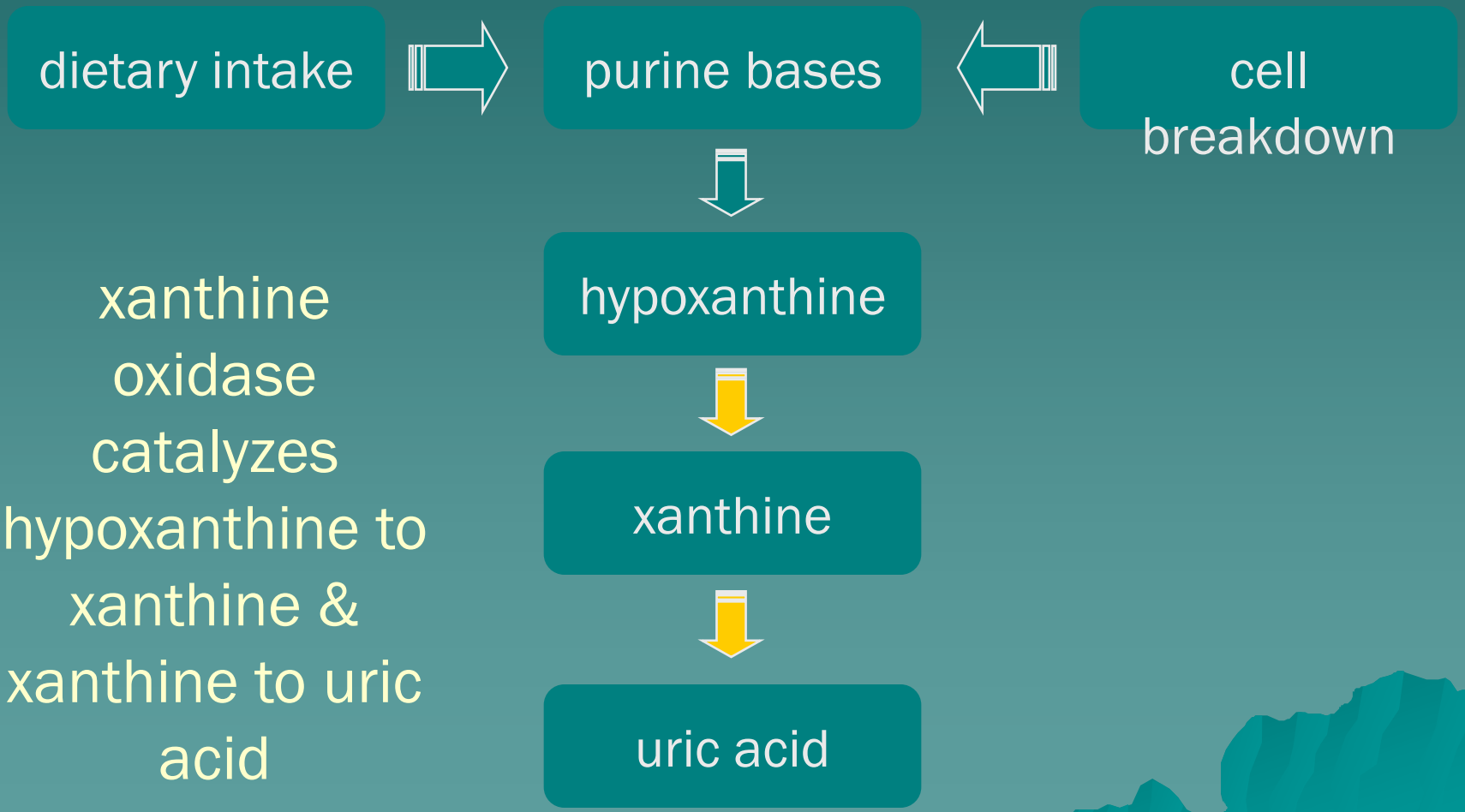


hyperuricemia results when production exceeds excretion

Hyperuricemia - mechanisms



Uric acid metabolism



xanthine oxidase catalyzes hypoxanthine to xanthine & xanthine to uric acid

Uric acid- poorly soluble - precipitated-deposited in cartilage of joints-inflammatory response to sodium urate crystals - infiltration of granulocytes-phagocytose - release glycoprotein - cartilage destruction

Drugs used to treat gout

Acute Arthritis Drugs

- colchicine
- steroids
- NSAID's

Chronic gout :Urate Lowering Drugs

- allopurinol
- probenecid

Colchicine - plant alkaloid

colchicum autumnale

(autumn crocus or meadow saffron)

Colchicine

- "only effective in gouty arthritis"
- not an analgesic
- does not affect renal excretion, production of uric acid

- Mechanism of action

- Inhibits migration of granulocytes to inflamed area and release of glycoprotein

- Binds to microtubules ,arrest division in metaphase

Adverse effects

- gastrointestinal -nausea, vomiting, cramps, diarrhea, abdominal pain
- hematologic -agranulocytosis, aplastic anemia, thrombocytopenia
- muscular weakness
- Dose 0.5-1.5mg/day

- **NSAIDs**- relieve acute attack
- Indomethacin
- Piroxicam
- Diclofenac
- Naproxen

Preferred over colchicine –better tolerated

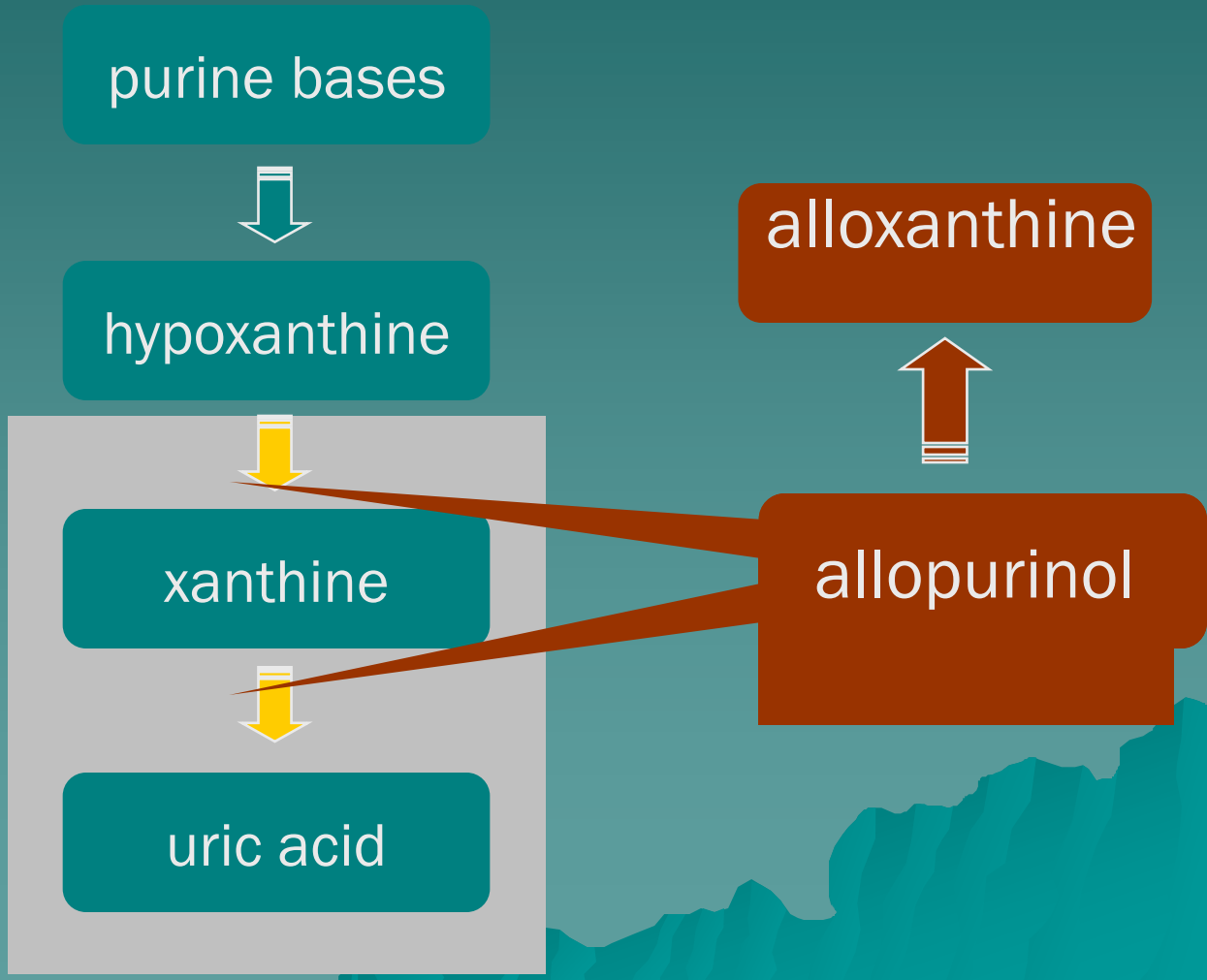
Glucocorticoids

Intra-articular injection

Not responding to NSAIDs

Allopurinol

allopurinol inhibits xanthine oxidase



Use

Chronic gout-First choice

100-300mg/day

To be given with NSAIDs to prevent the acute attacks of gouty arthritis

Probenacid

Uricosuric drug

Blocks tubular reabsorption of uric acid

Large amount of water –to be given

A/E- Dyspepsia

Sulphinpyrazone---- Not used

Febuxostat
Newer xanthine oxidase inhibitor
40-80mg /day