GOUT

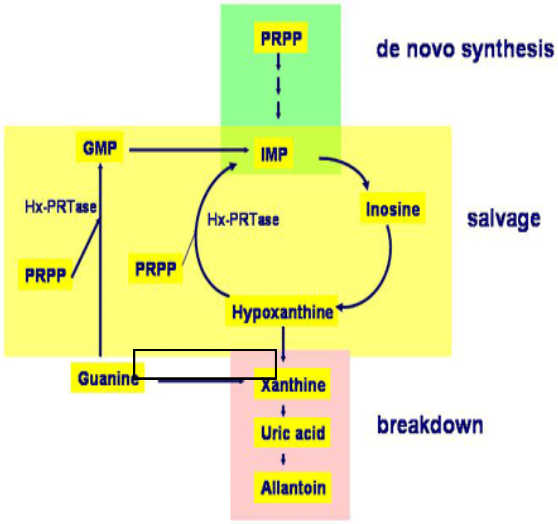
Definition:

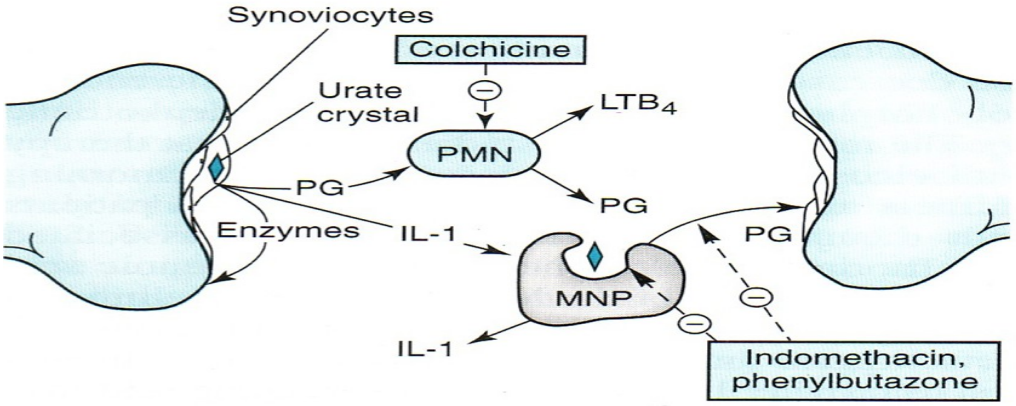
- Deposition of monosodium urate in joints and cartilage.
- Formation of uric acid calculi in the kidneys.

Pathophysiology:

- Uric acid increases in blood (hyperuricemia) because of overproduction and/or decreased excretion.
- Hyperuricemia doesn't always lead to gout, but gout is always preceded by hyperuricemia.
- Uric acid crystallizes in joints.
- Synoviocytes start the whole process by phagocytosing these crystals.
- This will lead to production of inflammatory mediators (prostaglandins PG, interleukin IL-1)
- The mediators will attract neutrophills and macrophages which phagocytose the crystals.
- This also will leads to production of more inflammatory mediators and this goes on and on.

*Why do other primates not develop gout?
b/c they have and additional ultimate uricase which degrades uric acid to the more soluble compound (allantoin.)





Drugs used in gout

Drugs that decrease urate production (uricostatic):
allopurinol

Drugs that increase urate excretion (uricosuric):
Probencid & sulfinpyrazone

Drugs that inhibit leukocytes migration:
colchicine

Drugs that have anti-inflammatory effect:
NSAIDs (indomethacin)

These drugs are not used individually when treating hyperuricemia!!

Drugs used in the treatment of gout and hyperuricaemia

1. *Acute attacks of gout*
   Non-steroidal anti-inflammatory drugs, for example indomethacin
   Colchicine

2. *Long-term control of gout or hyperuricaemia*
   Allopurinol
   Probenecid
   Sulphinpyrazone

ALLOPURINOL (PURINE ANALOG)

Mechanism of action:

- Inhibits the action of xanthine oxidase.
- Reduces the concentration of urate in blood and tissues.
- Reverses the deposition of urate crystals in tissues [tophi] & inhibits formation of renal stones [calculi].

PK:

- Oral absorption.
- $T1_{/2}$= 2-3 hrs (short)
- Allopurinol is further converted to the active metabolite alloxanthine with the long $t_{1/2}$= 18-30
- Excreted by filtration and secretion.

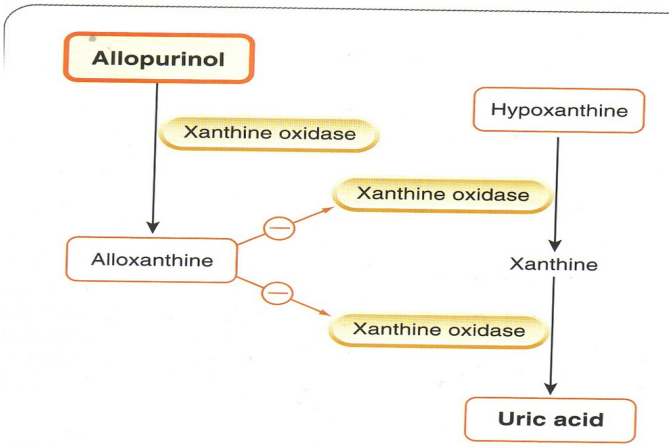


Fig. 16.4 Inhibition of uric acid synthesis by allopurinol. (See text for details.)

Adverse effects:

- Skin rash, is the main AE and is due to allergic reaction
- GI disturbances
- Acute attacks of gouty arthritis occur early in treatment when the drug induces reduction of the blood uric acid concentration, there will be a negative feedback absorption of uric acid from the tissues into the blood. Therefore, colchicine or NSAIDs should be administered concomitantly.

Drug interaction:

It ↑ the effects of mercaptopurine & azathioprine, cyclophosphamide by decreasing their elimination, oral anticoagulants & warfarin by inhibiting their metabolism.

Clinical uses:

- Chronic tophaceous gout
- in patients with gout whose 24-hour urinary uric acid on purine-free diet exceeds 600–700 mg.

in kidney problem:

- When probencid or sulphinpyrazone cannot be used
- Recurrent renal stone
- Renal impairment patients.
- Increased serum uric acid levels.

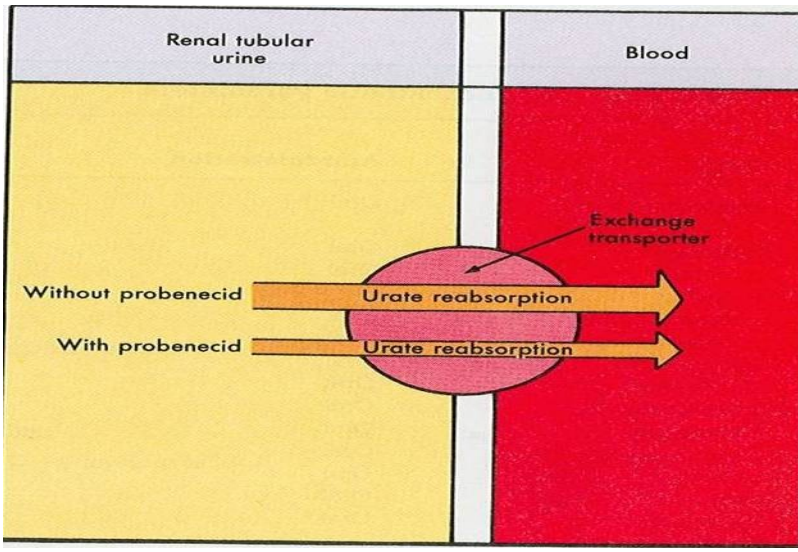
URICOSURIC AGENTS

Mechanism of action:

- Uric acid is filtered and actively secreted with 90% being reabsorbed by the proximal renal tubules.
- Uricosuric drugs are weak organic acids and, as such, act at the anionic transporter in the proximal tubules inhibiting uric acid reabsorption.

PROBENCID:

- Probenecid is completely reabsorbed by the renal tubules blocking uric acid reabsorption
- It is metabolized very slowly.
- $T1_{/2}$= 5-8 h
- Adverse effects: GI upset & rash



SULFINPYRAZONE

- Sulfinpyrazone or its active hydroxylated derivative is rapidly excreted by the kidneys.
- Adverse effects: nausea, aggravation of peptic ulcer, blood dyscrasias including aplastic anemia, but rare.

Clinical Indication for uricosuric agents:

1– have diminished renal clearance of uric acid
2– do not have renal stones or renal dysfunction
3– have had a previous reaction to xanthine oxidase inhibitor (if uricostatic is C/I).

- In a patient who excretes large amounts of uric acid, the uricosuric agents should be avoided.
- Urine volume should be maintained at a high level, and urine pH should be kept above 6.0. to maintain weak acid excretion.

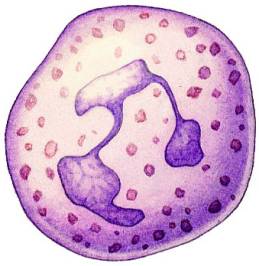
ASPIRIN

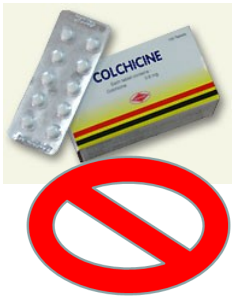
High doses: uricosuric + anti inflammatory
Low doses: inhibits urate secretion —> exacerbating hyperuricemia

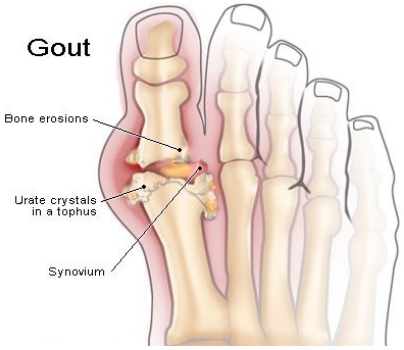
COLCHICINE

Mechanism of action:

- Binds to tubulin. Thus, inhibiting microtubule polymerization.
- This will interfere with the motility of neutrophills preventing migration.
- It also inhibits formation of leukotriene B4 (LTB_4)







PK:

- Oral absorption & IV
- Urinary and fecal excretion
- $T_{1/2}$= 9 h

Clinical uses:

- The antiinflammatory effect is used exclusively for gout.
- Prophylaxis for recurrent episodes of gouty arthritis

Adverse effects:

- Nausea, vomiting, abdominal pain, severe diarrhea (most important and is considered dose-limiting), hemorrhage, rash, kidney damage, and peripheral neuropathy.
- Since colchicine inhibits microtubules it will affect mitosis of other actively replicating cells similating antineoplastic drug adverse effects.

When choosing drugs for gout, first determine whether the patient gets chronic or acute attacks. Then find the cause of hyperuricemia, overproduction or undersecretion, or if there is a kidney disease. After that choose the drug is best for your patient.