Antigout Drugs

Subject: Pharmacology II
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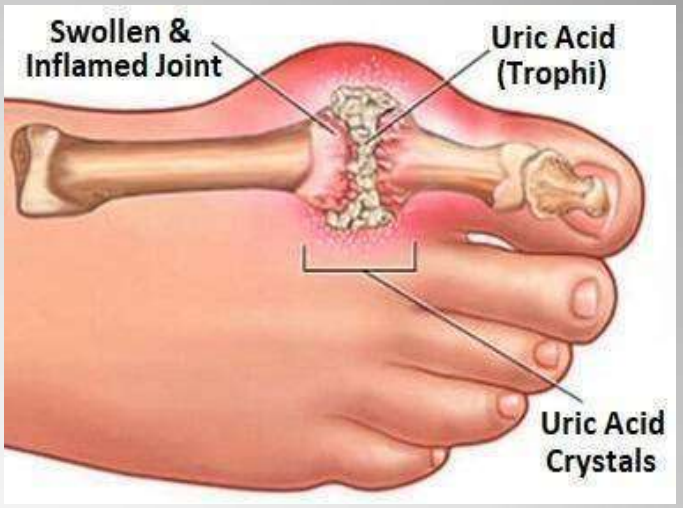
Introduction To Gout

Definition: Gout is metabolic disease in which plasma urate concentration get increased (hyperuricaemia),
(Normal urate level: 1-4 mg/dl).



Uric acid is product of purine metabolism at low pH (acidic) has low water solubility. When urate level increases in blood it gets precipitates and deposits in joints, kidney and cutaneous tissue.

Causes:

- Overdrinking of alcoholic beverages, especially beer, or purine-rich foods.
- Leukaemia's, lymphomas, polycythaemia condition treated with chemotherapy radiation causes enhanced nucleic acid metabolism and uric acid production.
- Drug like thiazides, furosemide, pyrazinamide, ethambutol, levodopa, clofibrate reduce uric acid excretion by kidney and produces gout.

Antigout drugs

These are the drugs which are used in treatment of gout condition which are acts by one of the following mechanism: By

- Inhibiting Uric acid synthesis (Allopurinol).
- Increasing Uric acid excretion (Probencid, Sulfinpyazone).
- Inhibiting leukocyte migration toward joint (Colchicine).
- Providing general NSAID's action (Glucocorticoids).

Classification

For acute gout: Acute gout is a painful condition that often affects only one joint. Drugs used are Ex- NSAID's, Colchicine, Glucocorticoids.

For chronic gout/ hyperuricaemia: Chronic gout is the repeated episodes of pain and inflammation. More than one joint may be affected Ex- Probencid, Sufinpyazone, Allopurinol

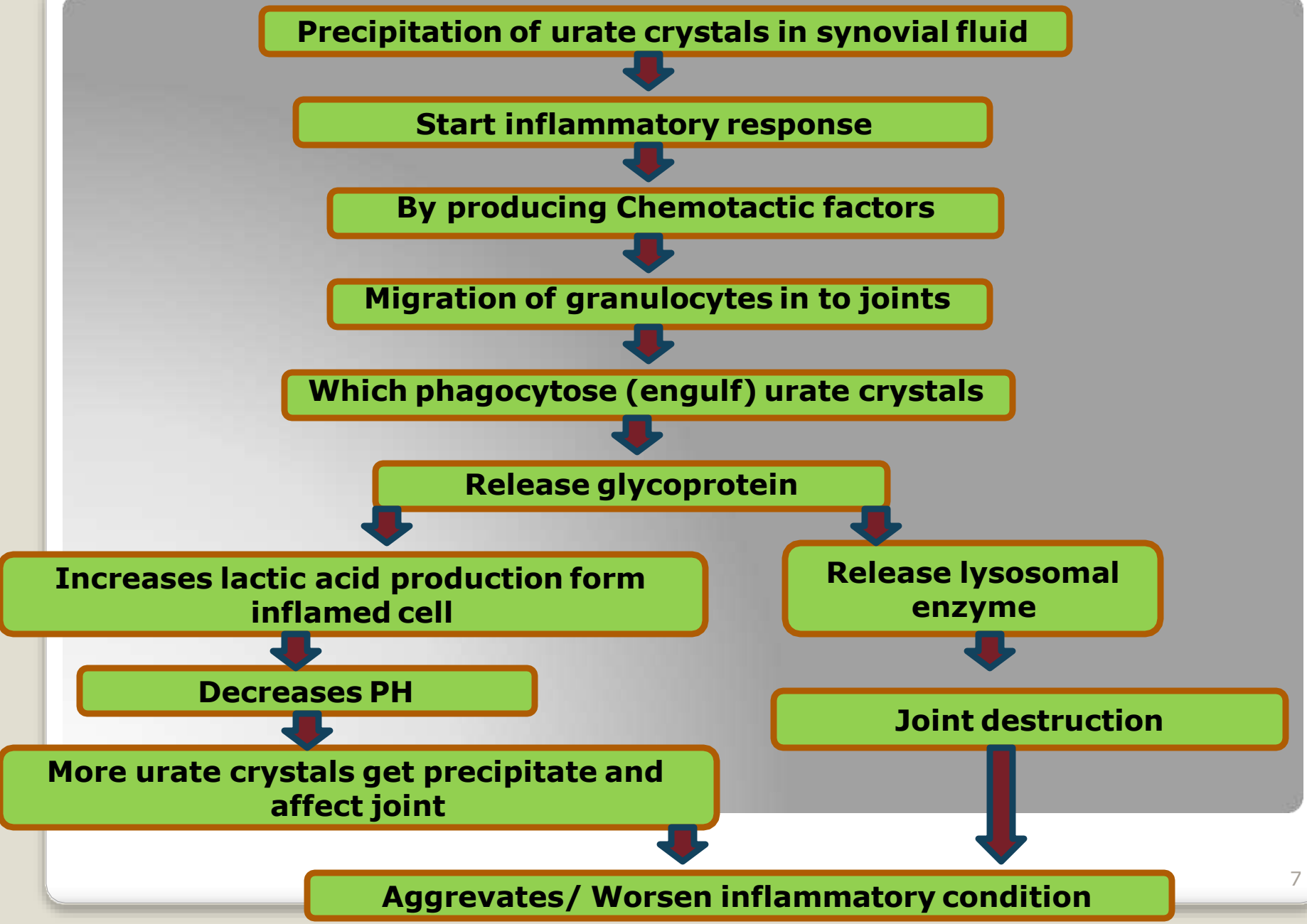
1. NSAID's drugs

- Various drugs used are indometahcin, piroxicam, diclofenac or etoricoxib given at high and repeated dose to terminate attack.
- Produces responses slow as compared to colchicine but well tolerated so more preferred than colchicine.
- Naproxen, piroxicam inhibits chemotactic migration of leucocytes into the inflamed joint.
- But not recommended for long term management due to risk of toxicity.

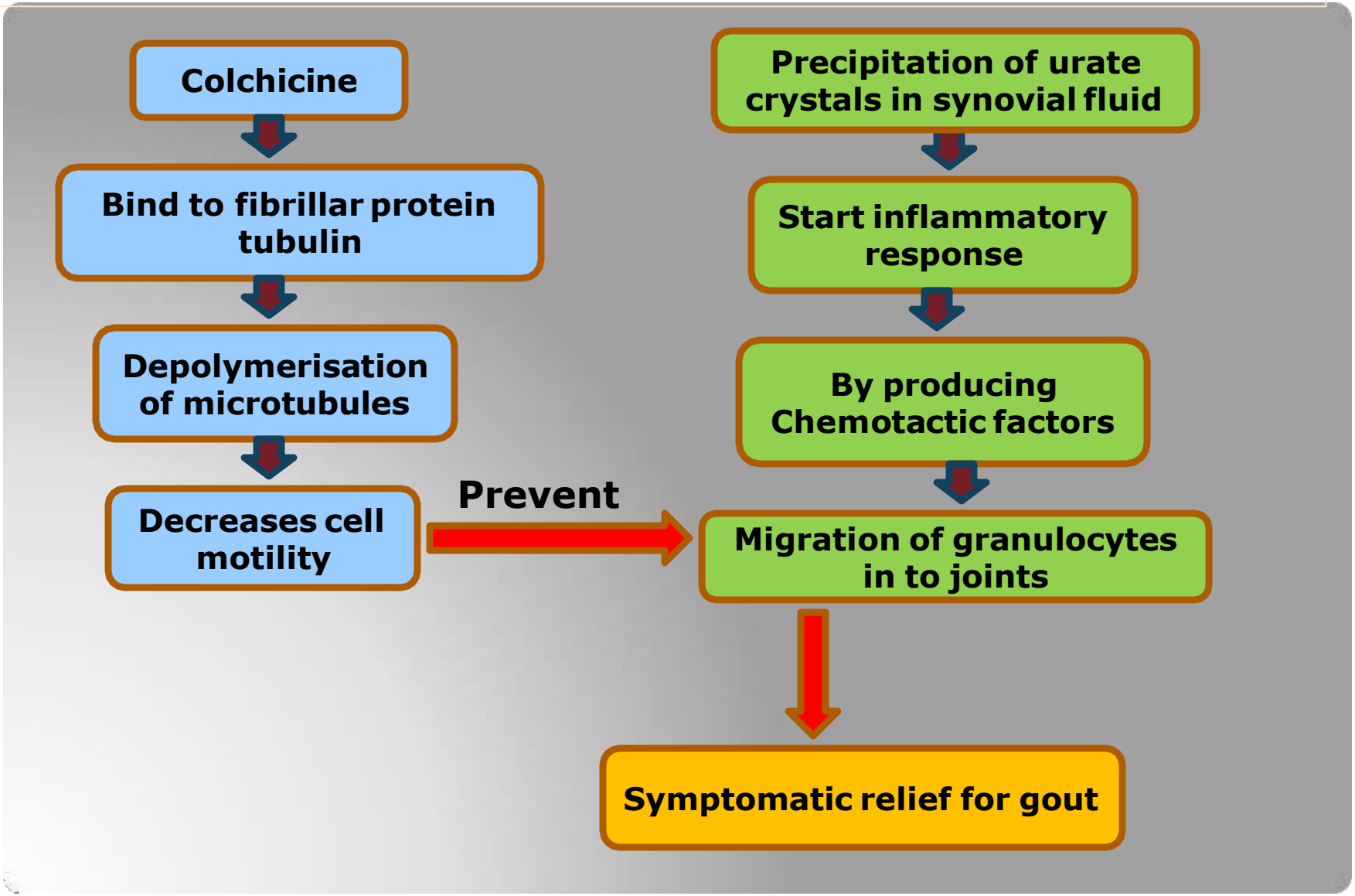
2. Colchicine

- Alkaloid from *Colchicum autumnale / autumn crocus* found as antigoute in 1763 and isolated as pure form in 1820.
- Not having anti-inflammatory or analgesic activity but used specifically in treatment of gouty inflammation.

* Process of gouty inflammation-



* Mechanism of action Colchicine:



Other actions of Colchicine:

Antimitotic: Binding to microtubules of mitotic spindle

↓ metaphase arrest ⟶ tried for cancer chemotherapy

↓ But causes toxicity.

Gut action: ↑ gut motility through neural mechanism.

Pharmacokinetics:

- **Absorption:** Rapid orally.
- **Distribution:** Uniform.
- **Metabolism:** Liver
- **Elemination:** bile-undergoes enterohepatic circulation, Urine & faeces.

*** Toxicity of Colchicine:** High and dose related.

At therapeutic dose: Nausea, vomiting, watery or bloody diarrhoea and abdominal cramps.

Accumulation of the drug in intestine and inhibition of mitosis .

In overdose: colchicine produces kidney damage, CNS depression, intestinal bleeding; death is due to muscular paralysis and respiratory failure.

Chronic therapy: Not recommended because it causes aplastic anaemia, agranulocytosis, myopathy and loss of hair.

* **Drug interaction with other drug:** Colchicine shows interaction with;

Sr . No.	Category of drug	Example from class	Interaction
1.	Cholesterol drugs	atorvastatin, fluvastatin, lovastatin, gemfibrozil	Serious muscle damage.
2.	Antiarrhythmic drug.	Digoxin,	
3.	HIV drugs,	indinavir, atazanavir, nelfinavir, saquinavir, or ritonavir.	
4.	Antidepressressants	nefazodone.	
5.	Antibiotics,	clarithromycin or telithromycin	
6.	Antifungal drugs	ketoconazole or itraconazole.	Increases concentrationof colchicine
7.	Calcium channel blocker	verapamil or diltiazem	stomach pain, constipation, diarrhea, nausea, or vomiting.

* Use of Colchicine:

1. **Treatment of acute gout:** Best drug to control an acute attack of gout, 1 mg orally followed by 0.25 mg 1-3 hourly till control of the attack.

2. **Prophylaxis condition of gout:** Colchicine 0.5-1 mg/day prevent gout attack but now a days NSAID's are preferred.

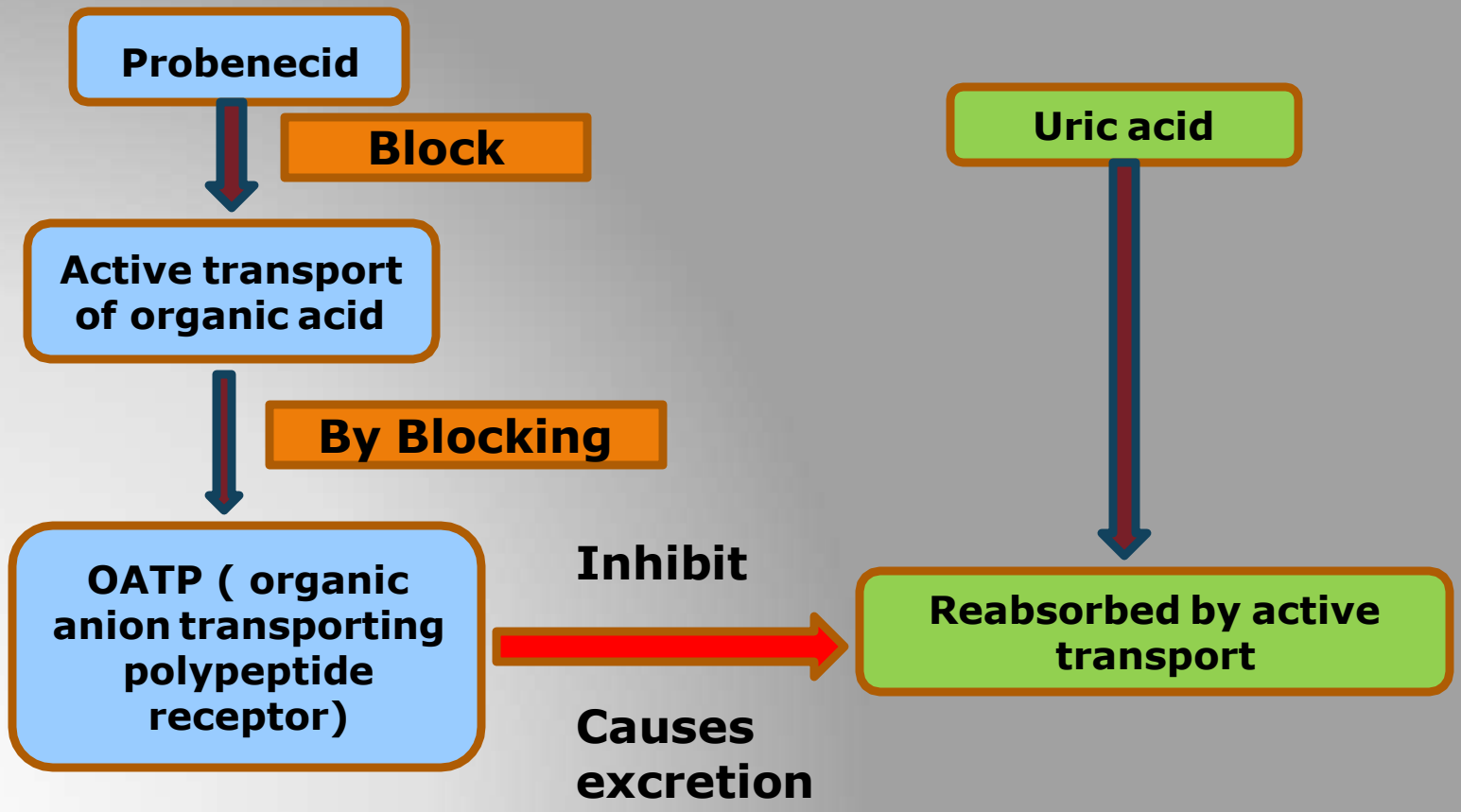
3. Corticosteroid

- Intraarticular injection of soluble steroids suppress symptoms of acute gout.
- Corticosteroids decrease the pain, swelling, redness and (inflammation) of gout.
- But Corticosteroids are used only for patients suffering from renal failure or peptic ulcer(Bcause NSAID's are contraindicated).
- Risk of rebound of attack is observed on drug withdrawal.
- Example; Prednisolone 40-60 mg given once a day.

4. Probenecid

- Lipid soluble organic acid developed in 1951.

***Mechanism of action Probenecid:**



*Pharmacokinetics:

- **Absorption:** Rapid orally.
- **Distribution:** 90% bound to plasma protein
- **Metabolism:** Liver
- **Elimination:** Urine.

***Drug interaction with other drug:** Probenecid shows interaction with;

Sr . No.	Category of drug	Example from class	Interaction
1.	Antibiotics	penicillins, cephalosporins, sulfonamides,	Inhibits the urinary excretion
2.	NSAID's	Indomethacin, salicylates	
3.	Antibiotics	rifampicin.	Biliary excretion
4.	Antimicrobial	nitrofurantoin	Inhibits tubular secretion of drug

* Toxicity of Probenecid :

Dyspepsia (indigestion).
Rashes and other hypersensitivity .
Toxic doses cause convulsions and respiratory failure.

* Use of Probenecid:

Chronic gout and hyperuricaemia:

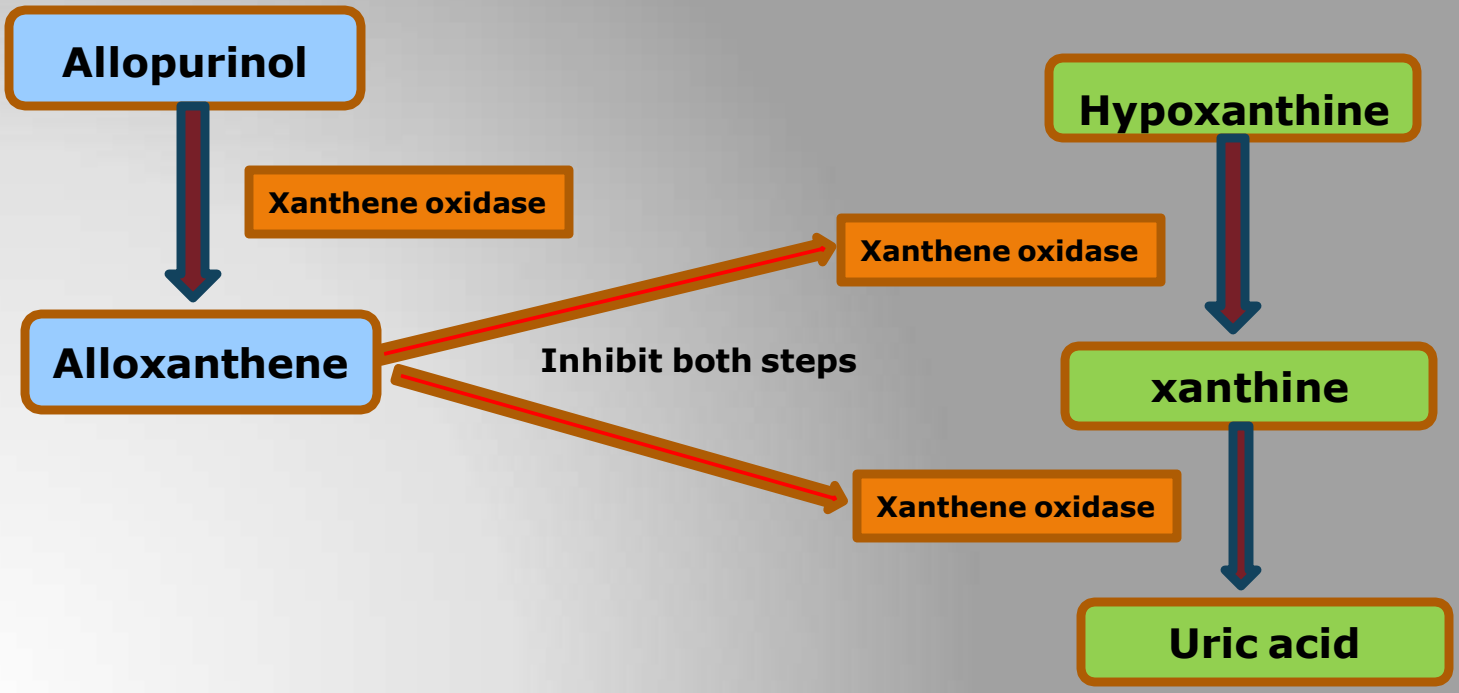
- second line or adjunct drug to allopurinol.
- 0.25 g-0.5g BD gradually lower blood urate level along with arthritis, and other lesions but ineffective during renal insufficiency.
- Plenty of fluids should be given with probenecid to avoidurate crystallization in urinary tract.

Prolong drug action:

- Probenecid is also used to prolong penicillin or ampicillin action by enhancing and sustaining their blood levels, e.g. in gonorrhoea, Subacute bacterial endocarditis (SABE).

Allopurinol

- This hypoxanthine analogue was synthesized a purine antimetabolite for cancer chemotherapy it had no antineoplastic activity.
- It has substrate as well as inhibitor of xanthine oxidase, the enzyme responsible for uric acid synthesis.



* Pharmacokinetics:

- **Absorption:** Rapid orally.
- **Distribution:** Not bound to plasma protein.
- **Metabolism:** During chronic administration inhibit self metabolism.
- **Elemination:** 1/3 excreted as unchanged form in urine.

***Drug interaction with other drug:** Allopurinol shows interaction with;

Sr . No.	Category of drug	Example from class	Interaction
1.	Anticancer	f 6-mercaptopurin & azathioprine	Allopurinol prevent degradation of all drugs
2.	Uricosurics	Probenecid	kidney or liver disease
3.	Anti asthmatic	theophylline	skin rashes
4.	Haematinics	Iron therapy	mobilization of hepatic iron stores

* Adverse effect of Allopurinol:

- Hypersensitivity- rashes fever, malaise and muscle pain.
- Stevens-Johnson syndrome(serious disorder of the skin and mucous membranes. painful red or purplish rash)
- Gastric irritation, headache, nausea and dizziness .
- Liver damage.

* Use of Allopurinol:

- Drug of choice in Chronic gout.
- To potentiate 6-mercaptopurine or azathiopurine- During cancer therapy and immunosuppressant therapy.
- In treatment of Kala-azar- Inhibit leishmania by altering purine metabolism.