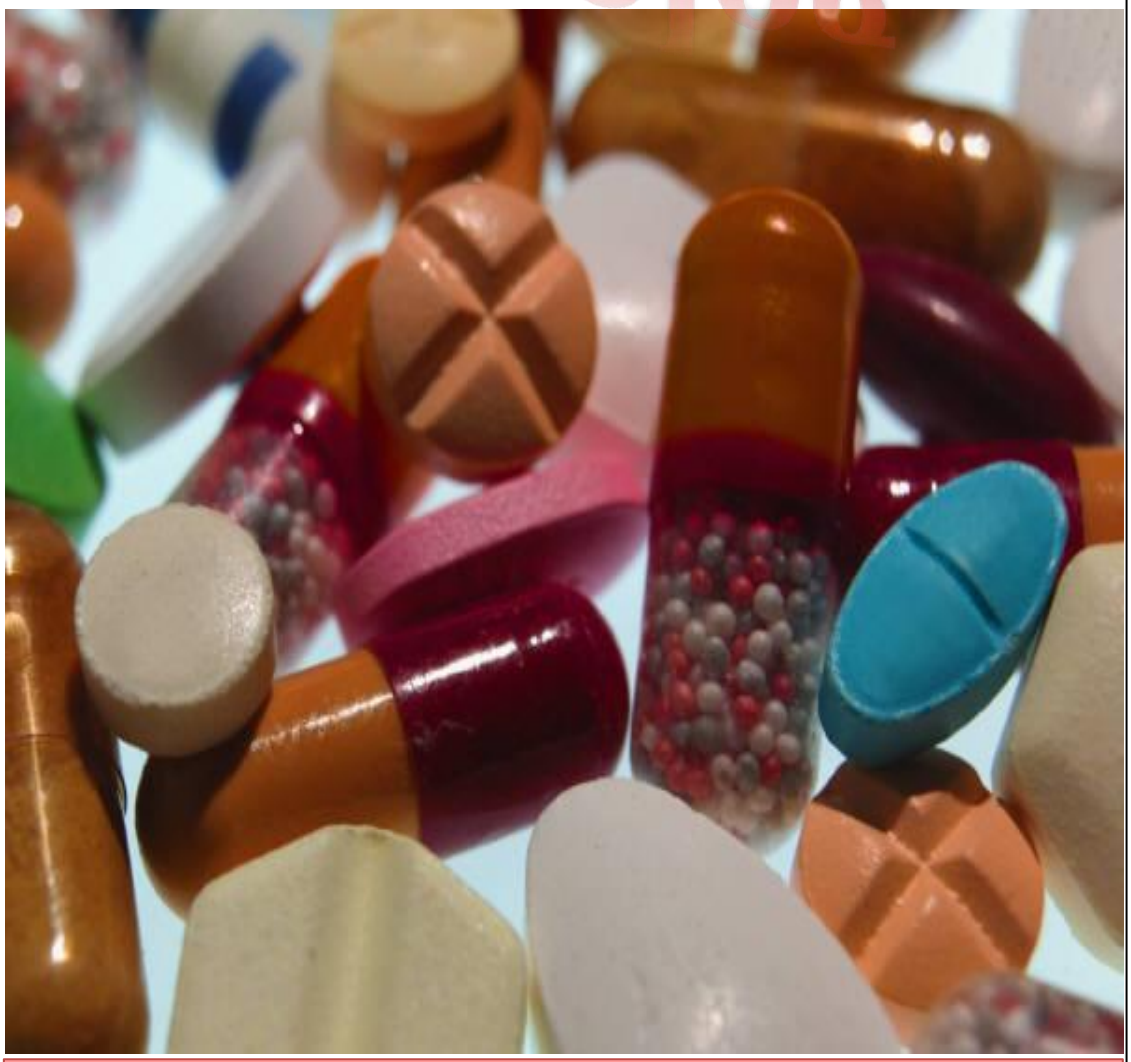
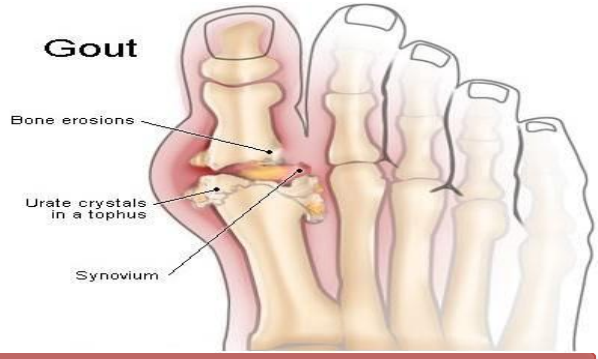
pharmacolog



By:.

Team of pharmacology

GOUT



- At the end of lectures students should:
- Define gout
- Describe outlines of treatment.
- Describe treatment of acute gouty arthritis
- Describe the mechanism of action, clinical uses & side effects of drugs used in acute attacks.
- Classify drugs used in chronic treatment.
- Define each group of drugs.
- Describe the mechanism of action, clinical uses & side effects & drug interactions for drugs used in chronic treatment.

What is GOUT? Oxford Dictionary:

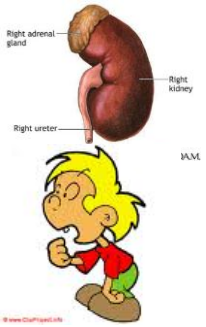
Disease in which a defect in purine metabolism causes ac excess of uric acid and it's salt (urates) to accumulate in the blood stream and the joint respectively.

It's result in attacks of acute gouty arthritis and chronic destruction of the joint & deposits of urates in the skin & cartilage, especially of the ears. The excess of urates also damages the kidney, in which stones may form. Treatment with drugs that increase the excretion of the urates (uricosuric drug or allopurinol), which slows their formation, can control the disease.

Acute attacks of gout are treated with anti-inflammatory analgesic.

- Blood → monosodium urate
- High blood uric acid level

- Most uric acid is excreted by kidneys
- ♂>♀
- Rare before puberty



Impaired uric acid excretion secondary to thiazide diuretics, chronic. Renal failure

Increase uric acid production due to increased cell turn over (tumours), increase uric acid synthesis (specific enzyme defect)

Idiopathic decrease in uric acid excretion (75%)

Aetiology of raised uric acid level

High dietary purine intake

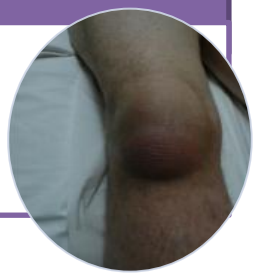
- Asymptomatic Stage
- Acute stage
- Intercritical stage
- Chronic stage

- have an elevated amount of uric acid within the body.
- the first official stage of gout.
- no outward symptomes.
- most of doctors do not feel need to treat.
- In many cases, a more appropriate to treat, to make an attempt to reduce the amount of uric acid.

Asymptomatic Stage

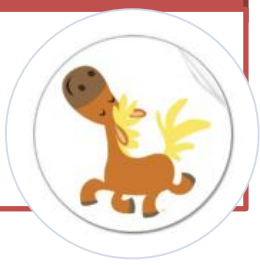
- the second stage of gout.
- the uric acid starts the process of crystallizing within the joint of the body.
- **symptomes would be:**
- inflammation within & around the joint.
- dicoloration of the skin.
- pain

Acute stage



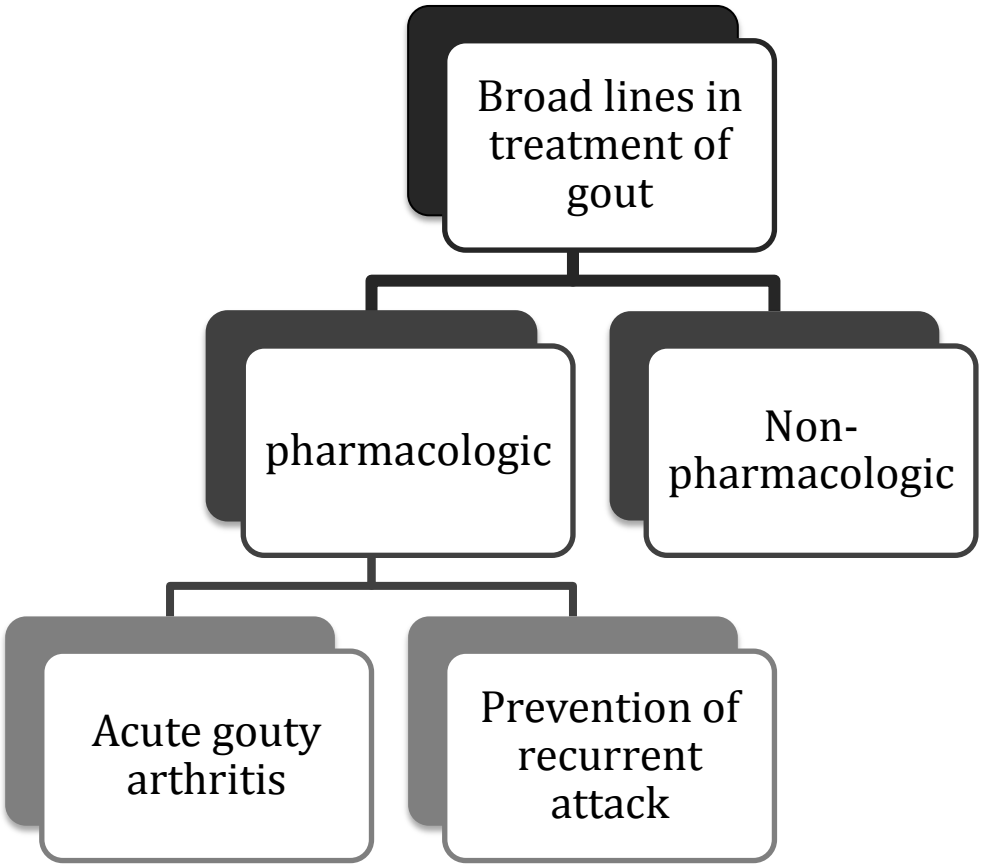
- the first stage of gout.
- symptoms-free period between attacks.
- joint functioning normally.
- is phase is frequently followed by continued attacksof gout.
- low level of inflammation may be associated with risks for heart disease and strok.

Intercritical stage



- the fourth stage of gout.
- it's the most chalenging.
- patient suffer from extented time before intering this particular stage.
- this stage is the most disabling.
- those patient will end up with damage in the joint an=or the inrnal organs.

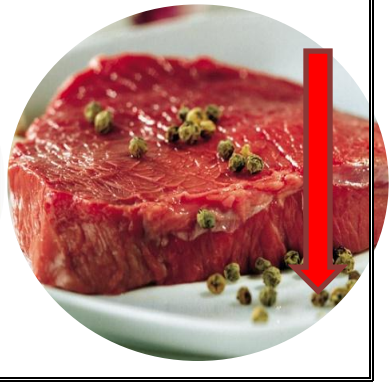
Chronic stage



Non-pharmacologic

Men in particular should limit their intake of alcohol, fats, and foods that are more likely to increase uric acid level in the body -- meat, sardines, bacon, mussels, and yeast. Alcohol, Such men should watch their weight with extra care. Drinking plenty of liquids may help minimize the risk of kidney stones.

CONTROL

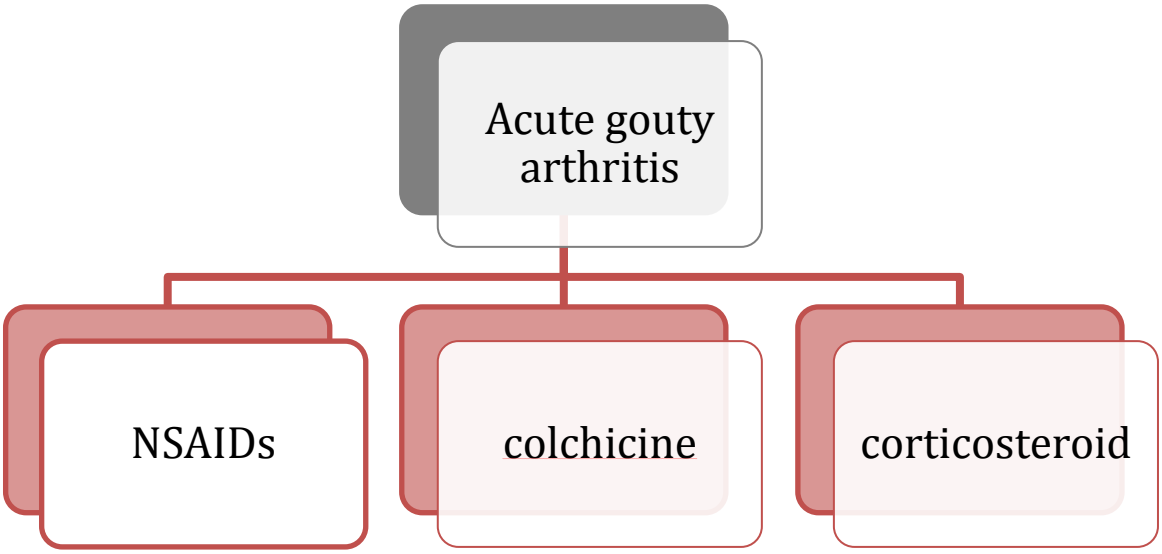


DRUGS USED IN TEATMENT OF GOUT

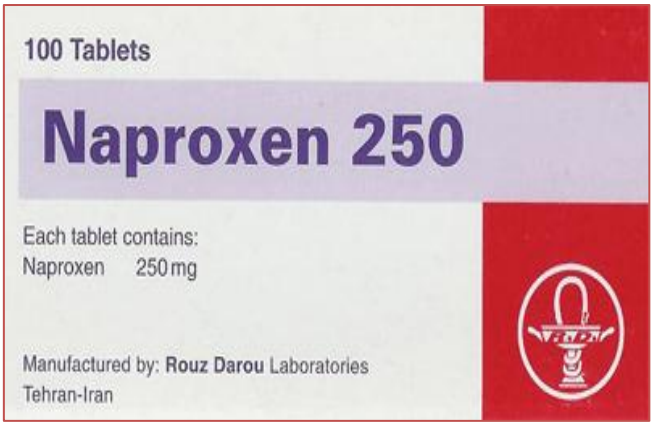
Most therapeutic strategies for gout involve lowering the uric acid level below the saturation point (<6 mg/dL), thus preventing the deposition of urate crystals.

This can be accomplished by:

1. Interfering with uric acid synthesis with *allopurinol*
2. Increasing uric acid excretion with *probenecid* or *sulfinpyrazone*
3. Inhibiting leukocyte entry into the affected joint with *colchicine*,
4. Administration of NSAIDs



NSAIDs:

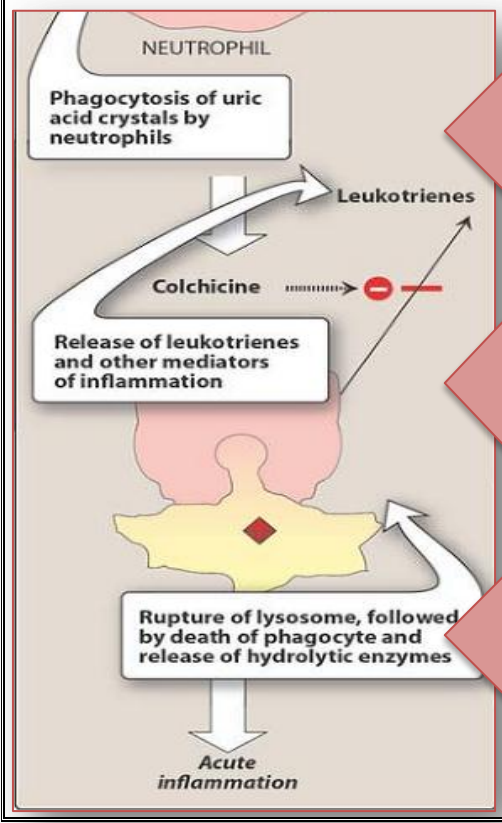


- Drugs of choice for young, healthy adults without any other serious medical condition.
- Usually taken orally at their highest safe dosage as long as gout symptoms persist and for three or four days after.
- Low doses of NSAIDs may be used to prevent gout attacks, including in patients who are starting anti-hyperuricemic therapies.

Colchicine:

- A plant alkaloid
- Used for the treatment of acute gouty attacks and prophylaxis
- Neither a uricosuric nor an analgesic agent, yet relieves pain in acute attacks of gout
- Prophylactic effect which reduces the frequency of acute attacks

MECHANISM OF ACTION



Binds to tubulin > disrupt mobility of granulocytes to affected area

Inhibits the synthesis and release of the leukotrienes B_4 and interleukin-8

Decrease production of TNF-α by macrophages

PHAPHARMACOKINETICS

- Administered orally, followed by rapid absorption from the GI tract
- Reaches peak plasma levels within 2 hours
- Also available combined with *probenecid*
- Recycled in the bile and is excreted unchanged in the faeces or urine.
- Use should be avoided in patients with a creatinine clearance of less than 50 mL/min.

THERAPEUTIC USES

- The anti-inflammatory activity of *colchicine* is specific for gout, usually alleviating the pain of acute gout within 12 hours
- Colchicine is currently used for prophylaxis of recurrent attacks and will prevent attacks in more than 80% of patients.
- Treatment for Mediterranean Fever

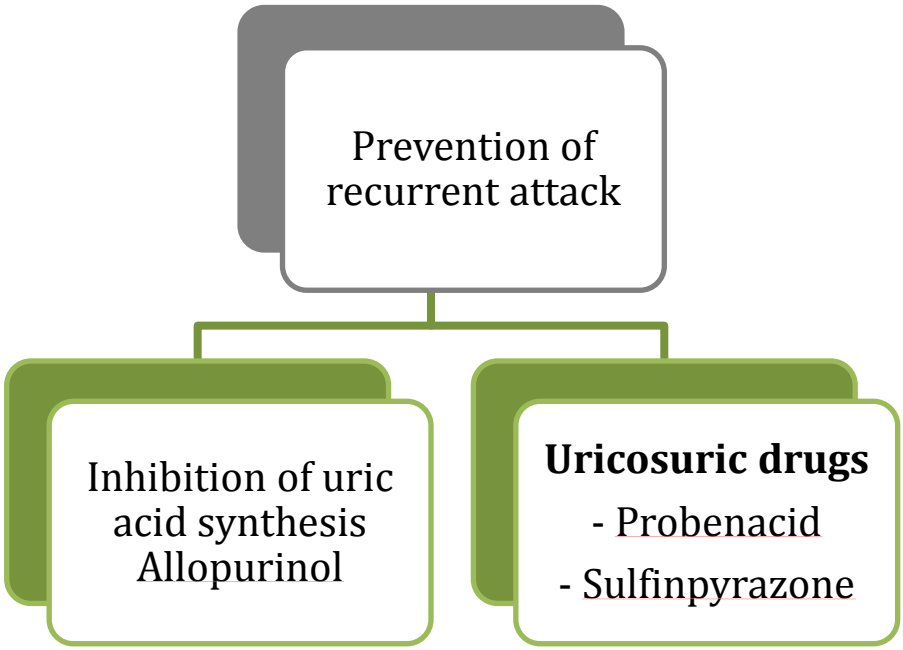
ADVERSE EFFECTS

- Diarrhea is a common adverse effect. May cause nausea, vomiting, and abdominal cramps.
- Chronic use may cause, alopecia, bone marrow depression, peripheral neuritis, and myopathy.
- Also, affect fertility

THE ALGORISM OF TREATMENT OF GOUT

If there is contraindication we use colchicine, if NOT we use NSAIDs, Then if there is no response, we look how many joint involved.

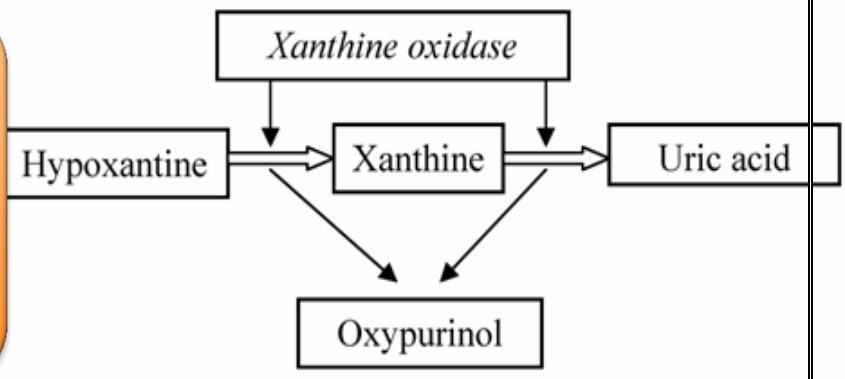
If it's just one so give the patient corticosteroid intra-articular, but if it more than one give him the corticosteroid orally or parentally.



Inhibition of uric acid synthesis:

MECHANISM OF ACTION

Allopurinol inhibits the xanthine oxidase to stop conversion of hypoxanthine to xanthine to inhibit the uric acid svnthesis.



PHARMACOKINETICS

Allopurinol is pro drug it has a short plasma half life, while it has long metabolize plasma half life.
So the main effect due to metabolize because it persist in the body for along time period. (Xanthine: High Solubility in water, uric acid:

THERAPEUTIC USES

- ❖ It is drug of choice in patient with both gout & coronary artery disease
- ❖ Severe tophaceous deposits (uric acid deposits in tissues)
- ❖ High serum uric acid in patients with impaired renal functions.
- ❖ Uric acid stones or nephropathy.
- ❖ Used to prevent increased uric acid levels in patients receiving cancer chemotherapy

SIDE EFFECTS

MOST COMMON	LESS COMMON
➢ Prolong and exacerbation ➢ an acute attack of gout ➢ Maculopopular skin rash ➢ Nausea, diarrhea	➢ Body: fever, headache ➢ CVS: vasculitis ➢ Hemic and Lymphatic: Thrombocytopenia ➢ Respiratory: Epistaxis

DRUG INTERACTIONS

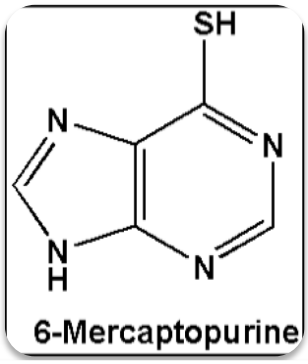
With oral anticoagulant:

warfarin

and

dicumarol

inhibits their metabolism



With anticancer :

Reduce the metabolism of

6-mercaptopurine

and **azathioprine**

Requring reduction of

Dosage up to 75%

With ampicillin :

Increases frequency

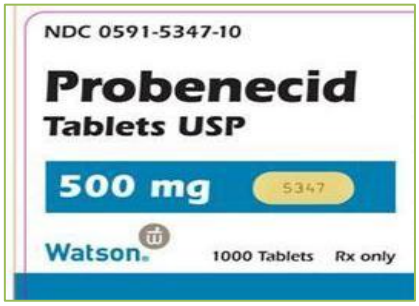
of **skin rash**

Prolongs half life of

Chlorpropamide

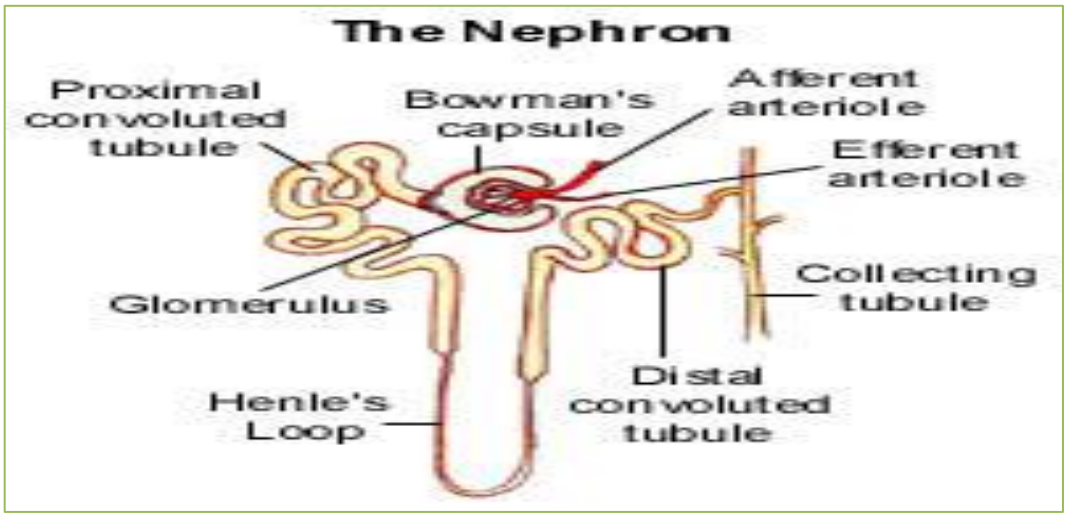
both compete for excretion in renal tubule

Uricosuric drugs:



MECHANISM OF ACTION

- Uricosuric drugs (probenecid, sulfinpyrazone, large dose of aspirin)
- Block the active transport sites of the proximal tubules (middle segment, decrease the reabsorption of uric acid & increase the amount excreted

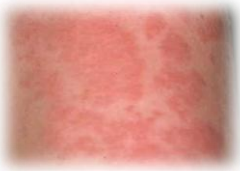


CLINICAL USES

- Chronic gout (urine volume should be maintained at a high level and urinary pH kept alkaline).
- Probenecid is used to prolong the action of some antibiotics e.g. penicillin.

SIDE EFFECTS

- Exacerbation of acute attack
- Risk of uric acid stone
- GIT upset
- Allergic rash



DRUG INTERACTIONS

- Aspirin can prevent probenecid from being fully effective
- Sulfinpyrazone can aggravate peptic ulcer disease
- Aspirin products can interfere with sulfinpyrazone's effects
- Sulfinpyrazone can enhance the action of certain diabetes medicines

ALWAYS AVOID ASPIRIN

Contra-indication

- Previous urinary tract stone
- Impaired renal function
- Recent acute gout
- Co-administration of low dose aspirin

Summary

- ❖ Gout is a form of arthritis that is characterized by sudden, severe attacks of pain, redness and tenderness.
- ❖ Gout is caused by deposits of uric acid crystals in the joint.
- ❖ Uric acid is a waste product formed from the breakdown of purines.

- ❖ Treatment of gout includes:
  - Treatment of acute attacks.
  - Prevention of future attacks.
  - Treatment of chronic gout.

- ❖ Drugs used for acute attacks includes:
  - NSAIDs (selective or non-selective).
  - Colchicine interferes with the migration of granulocytes to the site of inflammation & reduces the release and synthesis of leukotriens.

- ❖ Main adverse effects includes:
  - Diarrhea.
  - Skin rash.
  - Kidney, liver & CNS injury.

- ❖ Drugs used for chronic treatment includes:
  - Uricosuric drugs that increase urinary excretion of uric acid.
  - Probenecid & sulfinpyrazone.

- ❖ Their main adverse effects includes:
  - Gastrointestinal problems.
  - Skin rashes.
  - Leukopenia.

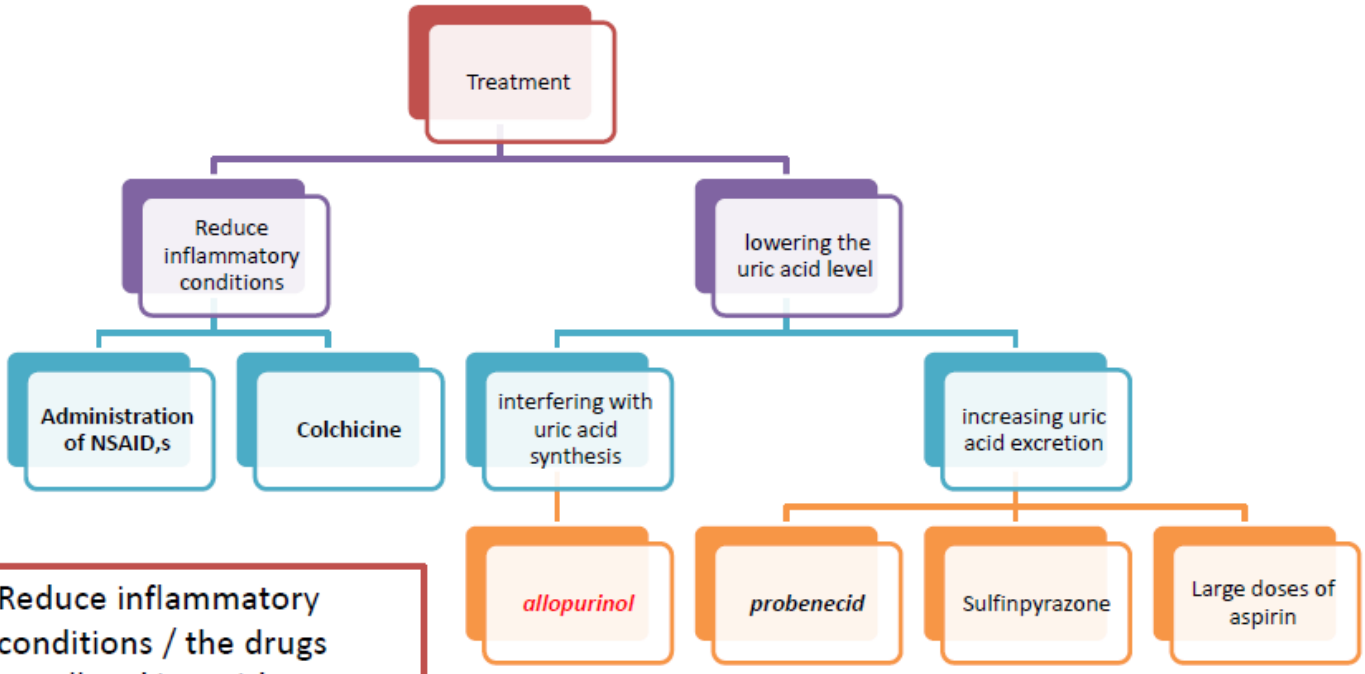
- ❖ Anti-hyperuricemic drugs that reduce the production of uric acid.

- ❖ Allopurinol is an oxidase inhibitor:
  - Used in patients with elevated blood uric acid level.
  - Or in patients with tendency for renal stone formation.

- ❖ Its main adverse effects includes:
  - Gastric problems.
  - Skin rashes.
  - Leukopenia.
  - Thrombocytopenia.

- ❖ Allopurinol reduces the metabolism of some drugs including azathioprime, this needs reduction of the doses of these drugs up to 75%

Note: lowering the uric acid level below the saturation point (<6 mg/dL), thus preventing the deposition of urate crystals.



Reduce inflammatory conditions / the drugs usually taking with acute stage