Pharmacology
team 436

MEDICINE
KING SAUD UNIVERSITY

Drugs in gout

Objectives:

- Know the pathophysiology of gout
- Outline the stages of gout and the therapeutic objectives in each stage
- Describe drug and non-drug treatment of gout
- Classify drugs used for treatment of gout
- Identify the mechanism of action of drugs used for treatment of gout
- Study in detail the pharmacology of drugs used for treatment of gout

ليس العار في أن نسقط، ولكنّ العار ألا نستطيع النّهوض

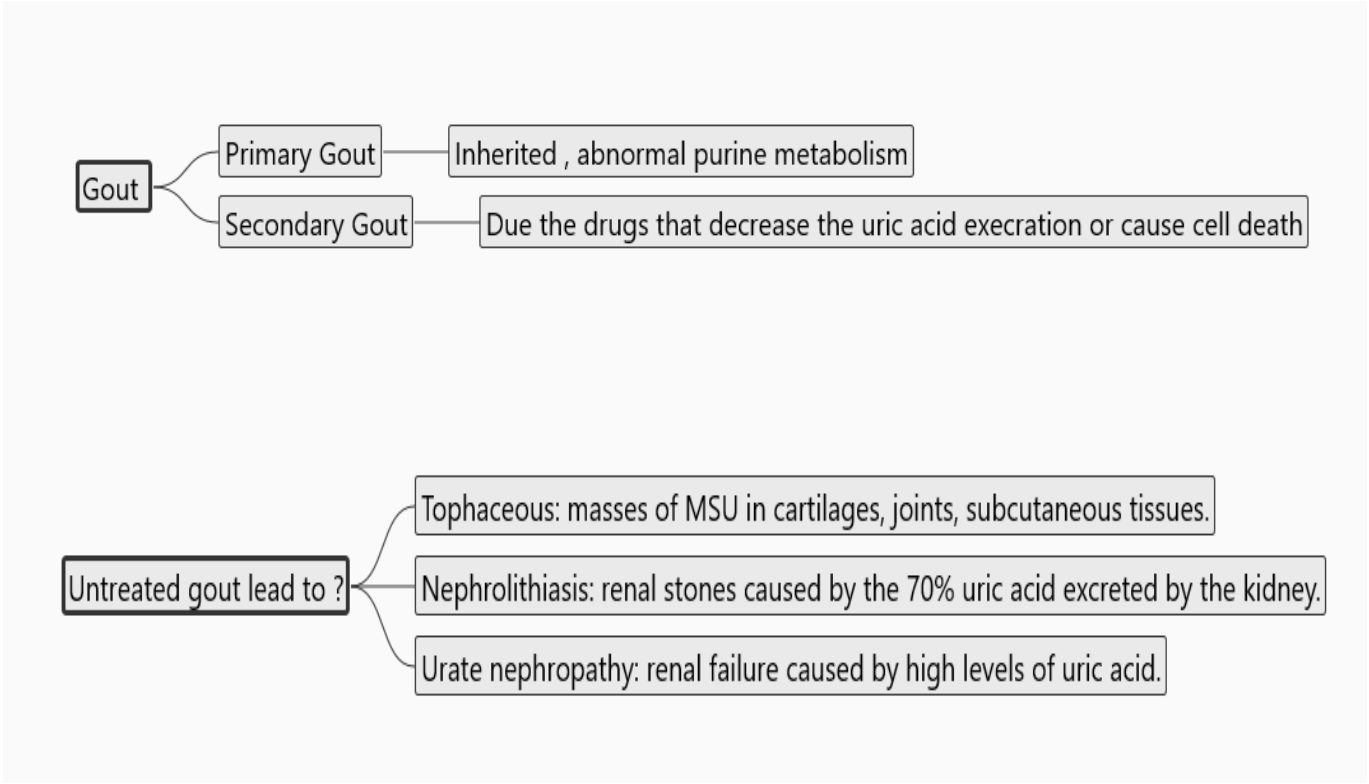
- Titles
- Very important
- Extra information
- Doctor's note

What is gout?

Gout is usually characterized by recurrent attacks of acute inflammatory arthritis with red, tender, hot and swollen joints

Pathogenesis:

Deposits of sodium urate crystals in articular, periarticular, and subcutaneous tissues



Epidemiology:

- Gout was historically known as "the disease of kings" or "rich man's disease."
- Prevalence of hyperuricemia 5%
- Prevalence of gout 0.2%
- Male to female ratio 10:1

Pathophysiology

The uric acid is a waste product formed from the degradation of purines(NB) through the purines degradation pathway.

Purines → xanthine $\xrightarrow{\text{Xanthine oxidase}}$ uric acid

If there is abnormal production and/or execration of uric acid it will cause deposition of Monosodium Urate Crystals(MUC) in joints and this will initiate the inflammation and cause gout.

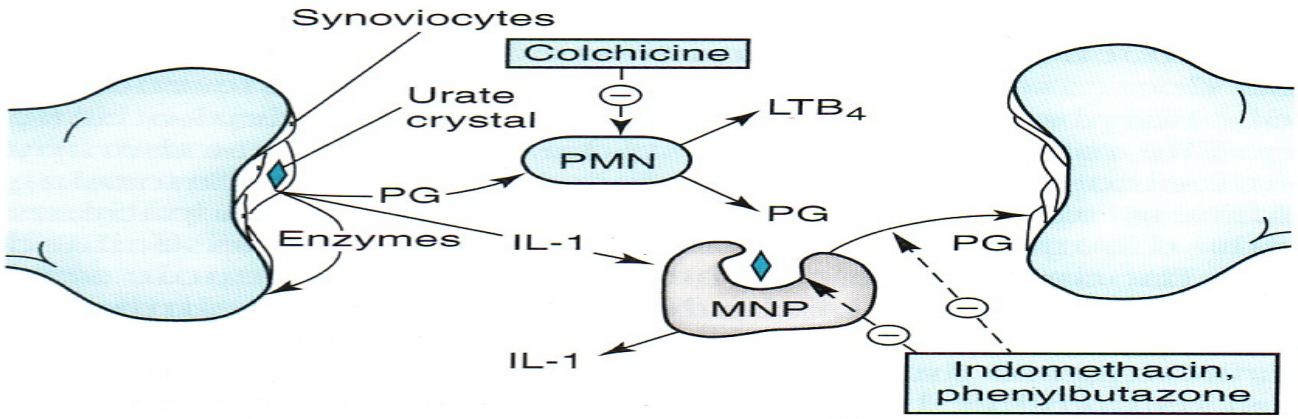
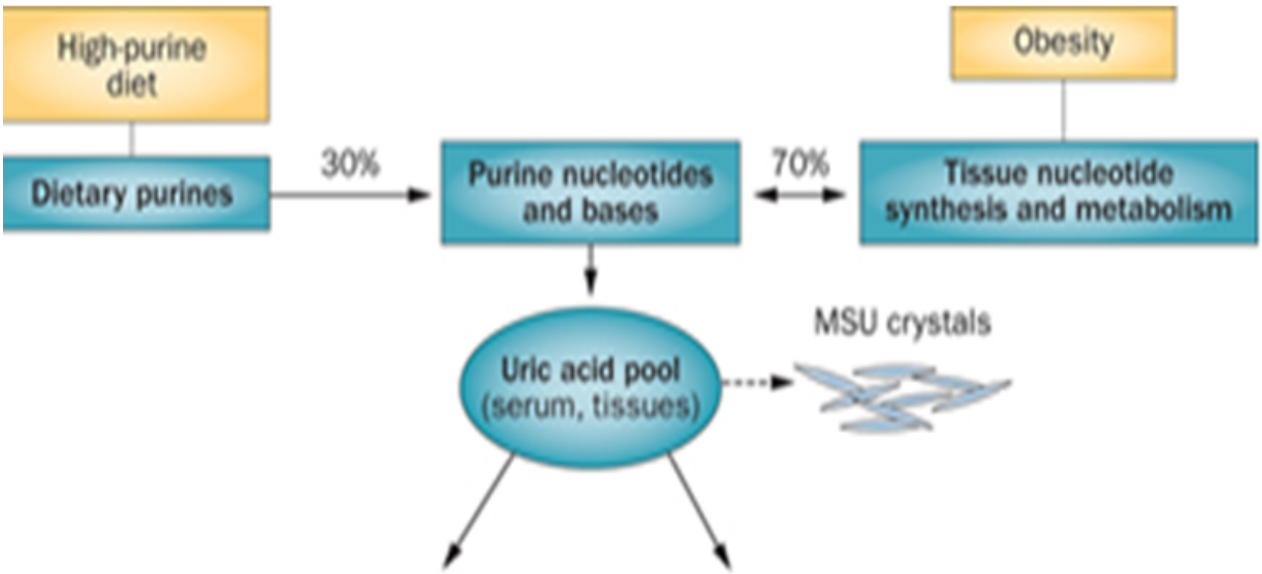
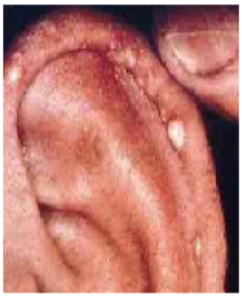


Figure 36–5. Pathophysiologic events in a gouty joint. Synoviocytes phagocytose urate crystals and then secrete inflammatory mediators, which attract and activate polymorphonuclear leukocytes (PMN) and mononuclear phagocytes (MNP) (macrophages). Drugs active in gout inhibit crystal phagocytosis and polymorphonuclear leukocyte and macrophage release of inflammatory mediators. (PG, prostaglandin; IL-1, interleukin-1; LTB4, leukotriene B4.)

Summary about gout





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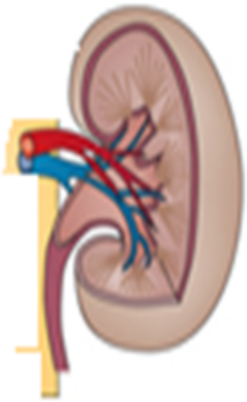
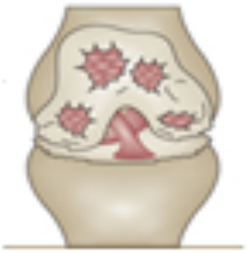


Nephrolithiasis



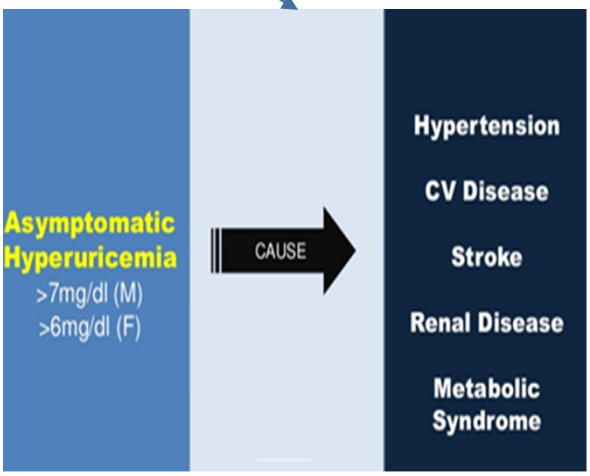
joint inflammation

Stages of gout

Stages of gout

asymptomatic hyperuricemia

Elevated serum urate with no clinical manifestation of gout



acute intermittent gout

acute inflammation in joint caused by free urate crystals
Management : Terminate the attack

Intercritical stage

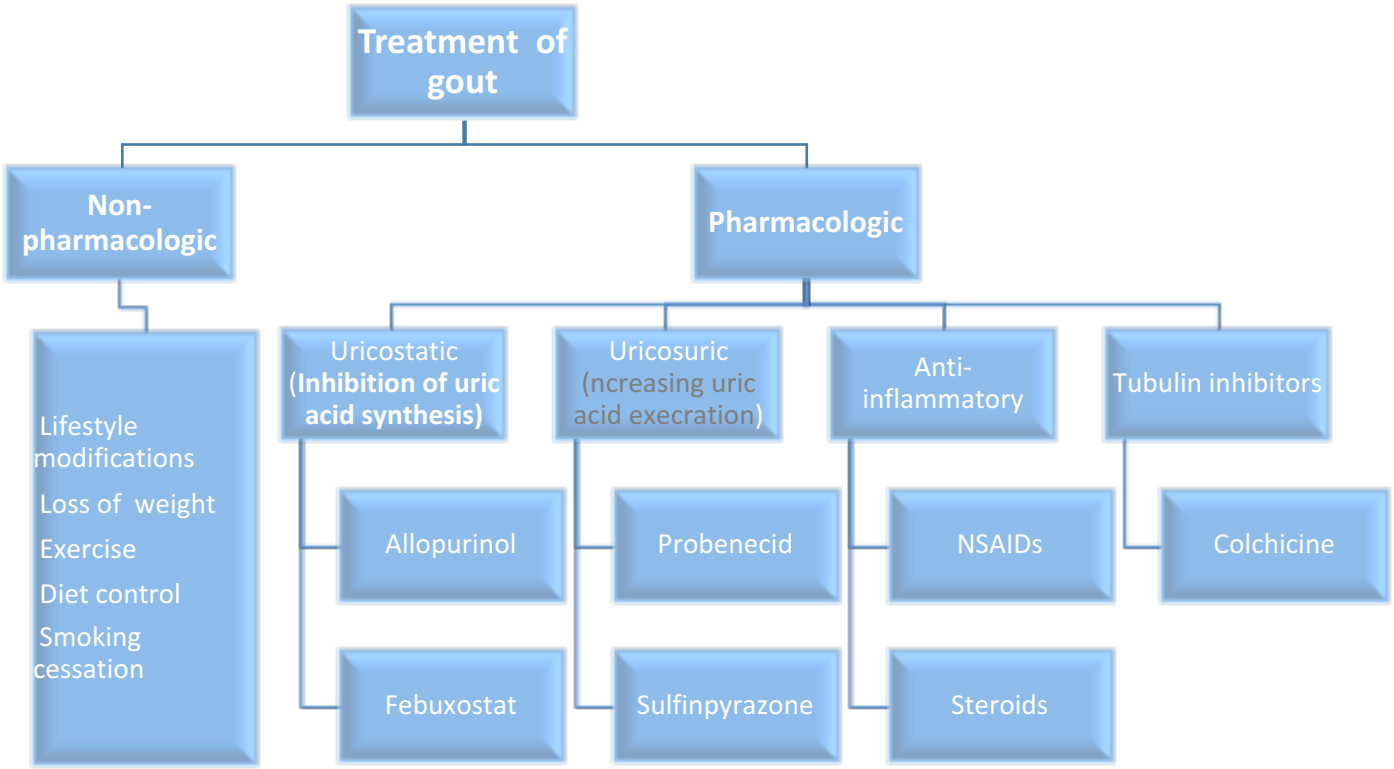
The intervale between acute flares
Management : Prevent recurrent attacks

chronic gout

Long-term gout complication
Management:
* Prevent complications
* Lower serum uric acid

In most cases diagnosis of gout is based on clinical presentation, which is quite characteristic: severe pain developing within hours, tenderness, warmth, swelling and erythema, e. g. in the first metatarsophalangeal or metacarpophalangeal joint. Frequently, gout flares up following rich meals and alcohol consumption, in the middle of the night.

Drugs in gout



Aim of pharmacotherapy:

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, Febuxostat
2. increasing uric acid excretion with probenecid or sulfinpyrazone
3. inhibiting leukocyte entry into the affected joint with colchicine
4. administration of NSAIDs

Treatment of acute gout

NSAIDS

- **NSAIDs are the most commonly used first-line treatment**
- **Head-to-head studies show few differences between drugs**
- **Full doses of NSAID should be initiated immediately**
- **and tapered after resolution of symptoms**
- **Should be avoid in:**
  - **GI ulcer**
  - **Bleeding or perforation**
  - **Renal insufficiency**
  - **Heart failure**
  - **Use of oral anticoagulants**

steroids

- Corticosteroids are a good alternative where NSAIDs
- and colchicine cannot be used or in refractory cases
- Studies showed equal efficacy between corticosteroid
- and NSAIDs, with no reported side-effects with
- short-term use of corticosteroids
- In elderly people, patients with liver or hepatic impairment, IHD (ischemic heart disease

), PUD (Peptic ulcer disease), hypersensitivity to NSAIDs

- Route of administration :
  - Intra articularly (preferred route if one or two joints affected)
  - Orally
  - Intramuscularly or intravenously.

Colchicine

Origin of this drug:
Alkaloid obtained from autumn crocus
The effect:
Minimal effect on uric acid synthesis , excretion & is not analgesic

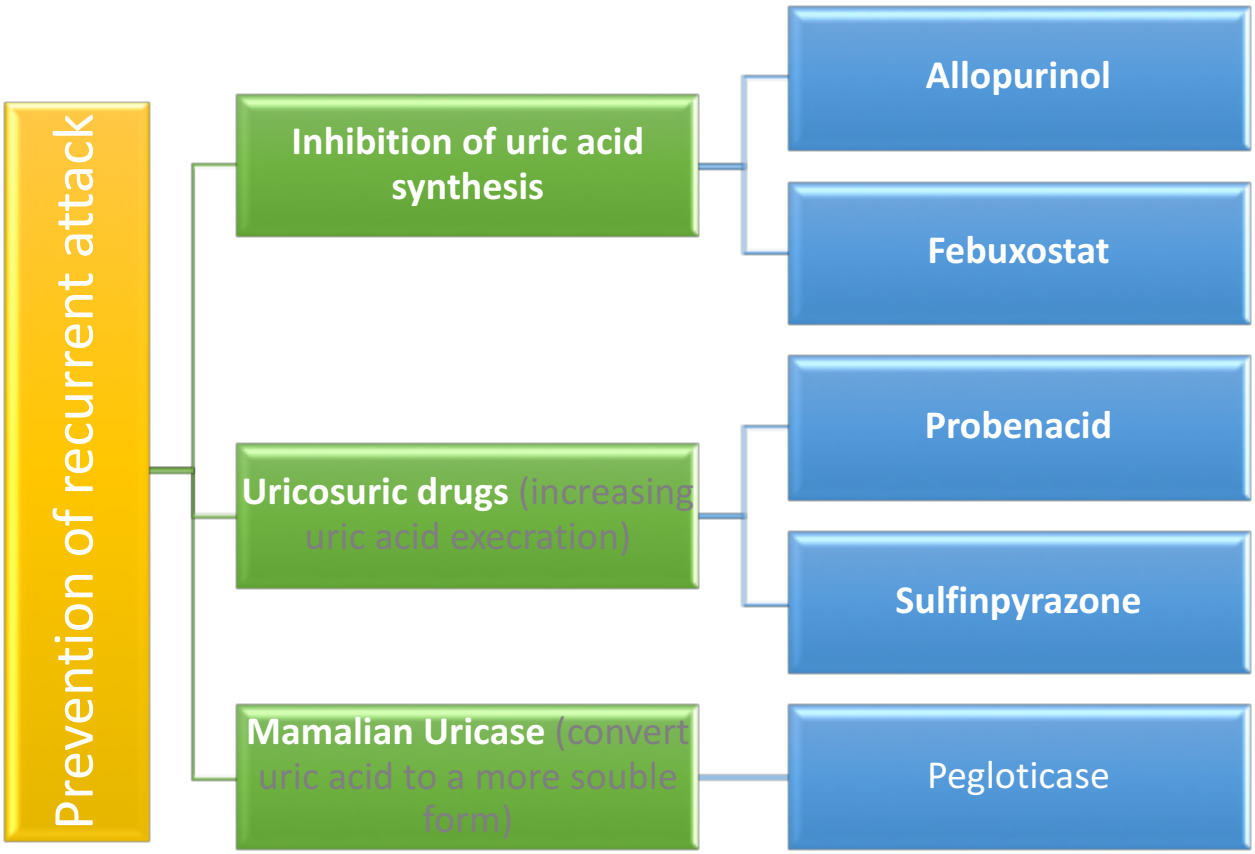
Mechanism:
Inhibits cell division by:
1- Inhibits chemotactic factors
2- Inhibits inflamosomes & IL-1 production

Pharmacokinetics:
Route of administration : orally
Absorption: rapidly absorbed from the GI tract
Half-life:
Reaches peak plasma levels within 2 hours
Rrecycling: in the bile
Excretion: unchanged in the faeces or urine
Should be avoid in : patients with a creatinine clearance of less than 50 mL/min

Clinical uses:
1- Treatment of gout flares
2- Prophylaxis of gout flares
3- Treatment of Mediterranean fever

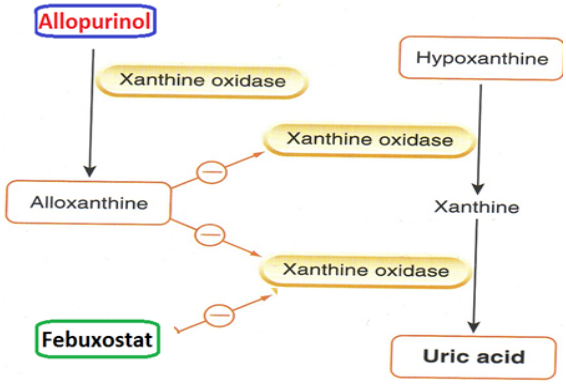
Side effect:
1- abdominal: Diarrhea (sometimes severe), Nausea and Vomiting, Abdominal cramps, Dehydration
2- immune: Bone marrow depression
3- cardiac: Cardiac toxicity, arrhythmia, Vascular collapse,
Hepatotoxicity , alopecia

Prevention of recurrent attack



Inhibitors of uric acid synthesis

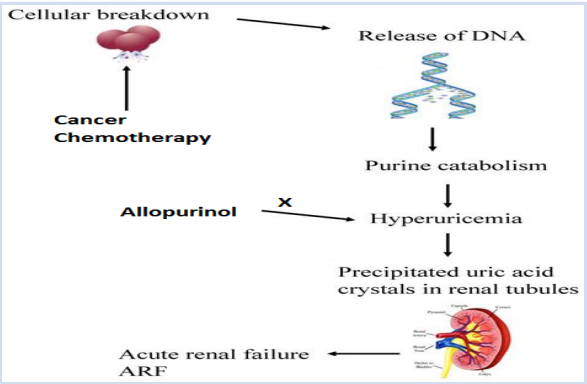
Mechanism of action: Inhibit xanthine oxidase
Pharmacokinetics:
Absorption: 70%
Protein binding: negligble 5%
Metabolism: Hepatic metabolism, 70% converted to active metabolite (oxypurinol) which eliminated unchanged in urine
ADRS (side effect):
1- Diarrhea, nausea, abnormal liver tests
2- Acute attacks of gout
3- Fever, rash, **toxic epidermal necrolysis** hepatotoxicity, marrow suppression vasculitis
4- DRESS syndrome (**D**rug **R**eaction, **E**osinophilia, **S**ystemic **S**ymptoms)
5- 20% mortality rate



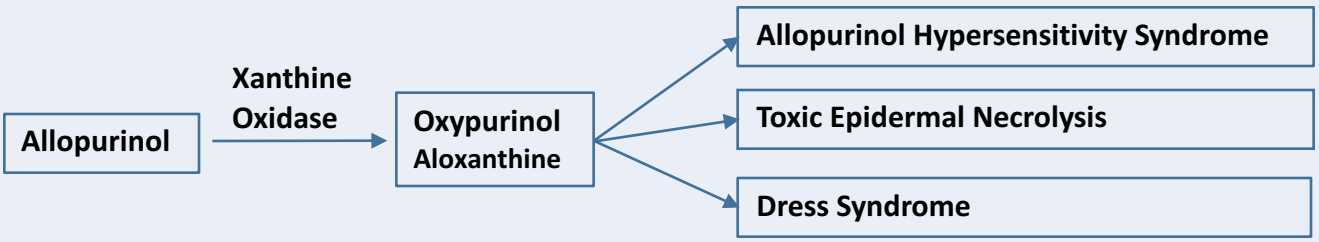
Allopurinol

Clinical uses:

- Management of hyperuricemia of gout
- Uric acid stones or nephropathy
- It is a drug of choice in patients with both gout & ischemic heart disease
- Severe tophaceous deposits (uric acid deposits in tissues)
- Management of hyperuricemia associated with chemotherapy
- Prevention of recurrent calcium oxalate kidney stones
- Metabolism: it is metabolized by xanthine oxidase into alloxanthine which is pharmacologically active

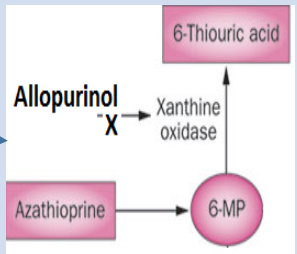


Side effect:



Drug Interactions:

- Warfarin & dicumarol: inhibits their metabolism
- 6-mercaptopurine and azathioprine: Reduce their metabolism **(so so imprtant)**
- ampicillin : Increases frequency of skin rash



Febuxostat

Clinical use: Indicated for the management of hyperuricemia in patients with gout (as it reduces serum uric acid levels)
* Chemically distinct from allopurinol (non purine)
* Can be used in patients with renal disease
* Oral specific xanthine oxidase inhibitor

Pharmacokinetics:
Route of administration: Given orally once daily
Absorption: well absorbed (85%)
Metabolism: Metabolized in liver , mainly conjugated to glucouronic acid
Protein binding: 99%
Half-life: (girl's slide: 8 hours) , (boy's slide: 4-18 hours)
* Given to patients who do not tolerate allopurinol

ADRS (side effect):
- Increases number of gout attacks during the first few months of treatment
- Increases level of liver enzymes
- Nausea, Diarrhea
- Numbness of arm or leg
- Headache

Uricosuric drugs

Uricosuric drugs

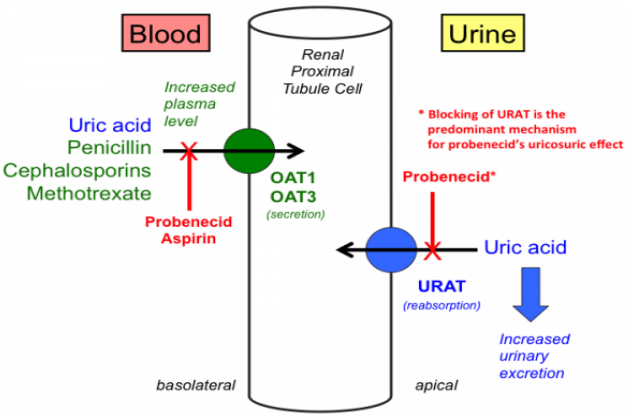
Mechanism:

Blocks tubular reabsorption of uric acid & enhances urine uric acid excretion

Probenecid inhibits Urate Transporters (URAT1) in the apical membrane of the proximal tubule

It also inhibits organic acid transporter(OAT)→↑plasma concentration of penicilin

Sulfinpyrazol inhibits URAT1 & OAT4



Effect:

Control hyperuricemia and prevent tophus formation

Probenecid moderately effective

Increases risk of nephrolithiasis

* Some drugs reduce efficacy (e.g., aspirin)

Contra-indications:

patients with renal disease

History of nephrolithiasis

Recent acute gout

Less effective in elderly patients

Probenecid

ADRS (side effect):

Exacerbation of acute attack

Risk of uric acid stone

GIT upset

Allergic rash

Sulfinpyrazone:

- Can aggravate peptic ulcer disease
- Aspirin reduces efficacy of sulfinpyrazone
- enhance the action of certain anti-diabetic drugs

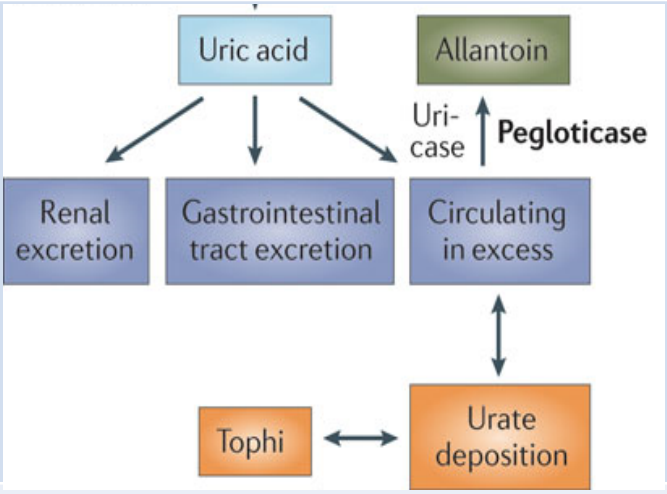
Recombinant mammalian uricase

Pegloticase

Mechanism of action:

1. A uric acid specific enzyme which is a recombinant modified mammalian uricase enzyme
2. enzymatically convert urate to allantoin, which is more soluble and readily excreted in the urine

allantoin كانها الن تلينين فتلين وتصير سايلة وتطلع من الجسم



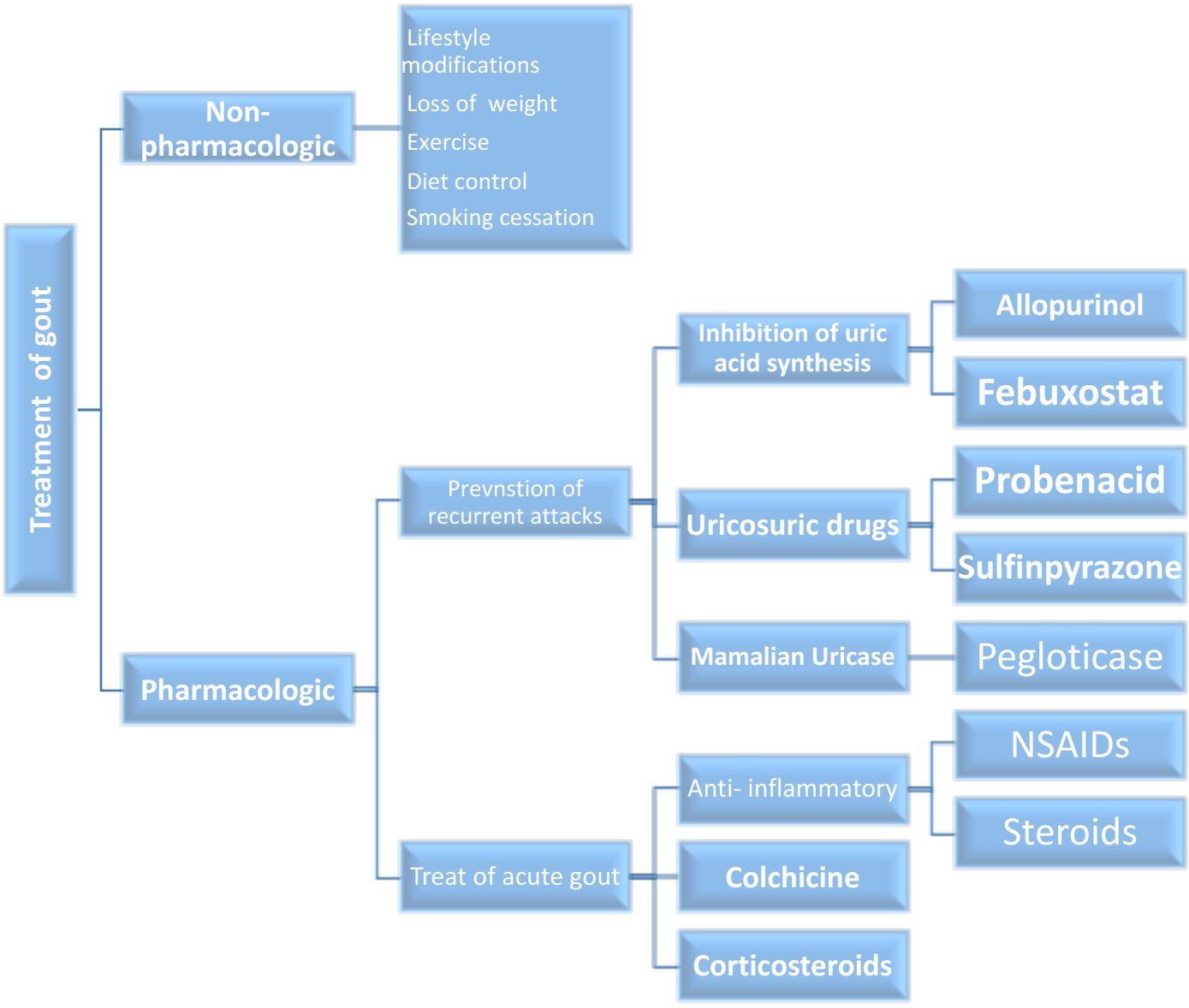
Clinical use:
Used for the treatment of chronic gout in adult patients refractory to conventional therapy

Route of administration: IV

Half-life:
peak decline in uric acid level within 24-72 hours

ADRS (side effect):
Infusion reactions
Anaphylaxis
Gout flare
Arthralgia (arthra: joints, algia: pain)
Muscle spasm
Nephrolithiasis

Treatment of gout



435 team

Summery of drugs in gout

Treatment of acute gouty arthritis

Drug	Mechanism	Contraindications, ADRs , uses
	most commonly used **first-line treatment** Full doses of NSAID should be initiated immediately and tapered after resolution of symptoms .	ADRs GI ulcer, Bleeding or perforation, Renal insufficiency, Heart failure, Use of oral anticoagulant.
Steroids (Corticosteroid)	Pharmacokinetics It can be given orally, IV, IM, or Intra-articularly . Has equal Efficacy with NSAIDs if the steroidal drugs used for a short period.	Used when NSAIDs are contraindicated or not tolerated. such as elderly people, patients with kidney or hepatic impairment, IHD, PUD.
	Natural product, obtained from autumn crocus. It was the first line of treatment of gout, but because it causes severe diarrhea, it limits its usage. It inhibits cell division, chemotactic factors, inflamosomes & IL-1 production. Pharmacokinetics: Given **orally**, Reaches peak plasma levels within 2 hours, Drug undergo enterohepatic recycling and is **excreted unchanged in the feces or urine.**	Uses: Treatment of gout flares Prophylaxis of gout flares. Treatment of Mediterranean fever Contraindications: renal impairment ADRs Diarrhea, Nausea, Vomiting, Alopecia, Abdominal cramps , Dehydration Bone marrow depression, Cardiac toxicity ,Arrhythmia Vascular collapse Hepatotoxicity

Prevention of gout recurrent attacks

Drug	Overview and Clinical uses	ADRS	Pharmacokinetics
Uricostatic drugs (inhibit uric acid synthesis by **inhibiting xanthine oxidase**)			
Allopurinol (purine)	• Management of hyperuricemia of gout (especially associated with chemotherapy) • Uric acid stones or nephropathy • It is a drug of choice in patients with both gout & ischemic heart disease • Severe tophaceous deposits • Prevention of recurrent calcium oxalate kidney stones • has a cardioprotective effect.	• Diarrhea, nausea, abnormal liver tests • Acute attacks of gout • Fever, rash, toxic epidermal necrolysis, hepatotoxicity, marrow suppression, vasculitis • **DRESS** syndrome • 20% mortality rate	**Drug Interactions** • ↑Warfarin , dicumarol & 6-mercaptopurine and azathioprine • With ampicillin : Increases frequency of skin rash • Absorption 70% • Protein binding negligible ,5%. • Hepatic metabolism, 70% metabolized by xanthine oxidase into **alloxanthine (oxyourinol) which is pharmacologically active**. eliminated unchanged in urine.
Febuxostat (non purine) more efficacious	• Indicated for the chronic management of hyperuricemia in patients with gout • can be used in patients with renal disease	• ↑ gout attacks during the first few months of treatment • ↑ liver enzymes • Nausea, Diarrhea • Headache • Numbness of arm or leg	• Given orally once daily, well absorbed(85%) • Metabolized in liver , mainly conjugated to glucuronic acid • Given to patients who do not tolerate allopurinol. • 99% protein bound • t½ = 8h
Uricosuric drugs (increase uric acid excretion by Blocking tubular reabsorption)			
Clinical use: Control hyperuricemia and prevent tophus formation			
Probenacid	ADRs: GIT upset, Exacerbation of acute attack, nephrolithiasis, Allergic rash.	Contraindications: History of nephrolithiasis, Recent acute gout, Existing renal disease, Less effective in elderly patients.	
Sulfinpyrazone	ADRs can aggravate peptic ulcer disease Increase risk of nephrolithiasis. Not used in patients with renal disease	Drug Interactions: Aspirin reduces efficacy of sulfinpyrazone enhance the action of certain antidiabetic drugs.	
Recombinant Mammalian uricase			
pegloticase	Used for the treatment of chronic gout in adult patients refractory (resistant) to conventional urate-lowering therapy.	ADRs Infusion reactions, Anaphylaxis, Gout flare, Arthralgia, Muscle spasm, Nephrolithiasis	Pharmacokinetics Converts uric acid to allantoin, which is more soluble and readily excreted in the urine. When Given by I.V, they produce peak decline in uric acid level within 24-72 hours

SAQ

A patient suffering from GOUT came to the hospital with extreme fatigue shortness of breath, he was later diagnosed with ischemic heart disease.

Q1: what is the recommended drug for his case ?
Allopurinol

Q2:Explain the mechanism of the used drug ?
Inhibit xanthine oxidase (act as Uricostatic drugs).

Q3: How is it metabolized and what its metabolite ?
It is metabolized by xanthine oxidase into alloxanthine which is pharmacologicaly active.

Q4: In which stage we can use this drug and what is the aim ?
Intercritical stage (Between Acute flares) to Prevent recurrent attacks.

Q5: Name a drug that could interact with it, and the resulted effect ?

- Warfarin & dicumarol → inhibits their metabolism
- Azathioprine → Reduce the metabolism
- Ampicillin → Increases frequency of skin rash

Q6:Give other clinical use for this drug :
Management of hyperuricemia associated with chemotherapy.

Q7: Give 2 adverse effects of the drug ?
Toxic epidermal necrolysis
DRESS syndrome (Drug Reaction, Eosinophilia ,Systemic Symptoms)

SAQ

A 76-year- old patient went to the hospital, with a history of acute renal failure, after few examinations,his uric acid level was above 6mg/dL.

Q1: What is the possible drugs that this patient can take?
Febuxostat

Q2 : What is the mechanism of action for the mentioned drug ?
Inhibit xanthine oxidase (act as Uricostatic drugs).

Q3: List two Anti-gout drugs we can not use it in this case (with patient with renal disease)?
Colchicine / Uricosuric drugs such as Probenacid & Sulfinpyrazone

A 55 lady with Acute gout came to the hospital with sever Diarrhea and Abdominal cramps. After taking her history we found that She in medication with Colchicine.

Q1 : What is the mechanism of action for the Colchicine as anti-gout drug ?
- Binds to microtubules in neutrophils
- Inhibits cell division
- Inhibits chemotactic factors
- Inhibits inflamosomes & IL-1 production

Q2: In which stage we can use this drug and what is the aim ?
Acute Falre of gout (during the attack) to Terminate the attack by inhibiting leukocyte entry.

Q3: Sever Diarrhea and Abdominal cramps are examples of ADRs for this drug. List three more ?
- Nausea & Vomiting
- Bone marrow depression
- Hepatotoxicity
- Cardiac toxicity, arrhythmia

QUIZ

تم بحمد الله ❤ ✌

Boys	Girls
عبدالرحمن ذكري	اللولو الصليهم
عبدالعزيز رضوان	روان سعد القحطاني
مؤيد أحمد	أثير الرشيد
فيصل العباد	سما الحربي
فارس النفيسة	نوره الشبيب
خالد العيسى	وتين الحمود
معاذ الفرحان	أمل القرني
عبدالرحمن الجريان	ابتسام المطيري
محمد خوجة	انوار العجمي
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