"بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ"

Drug Therapy for gout and management of hyperuricemia (MSS module)

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Objectives

✓Contrast the treatment of acute and chronic gout

✓ Drugs used for management of an acute attack of gout (e.g. colchicine, certain NSAIDs & glucocorticoids).

✓ Drugs used for the long-term management of gout (uricosuric agents & allopurinol)

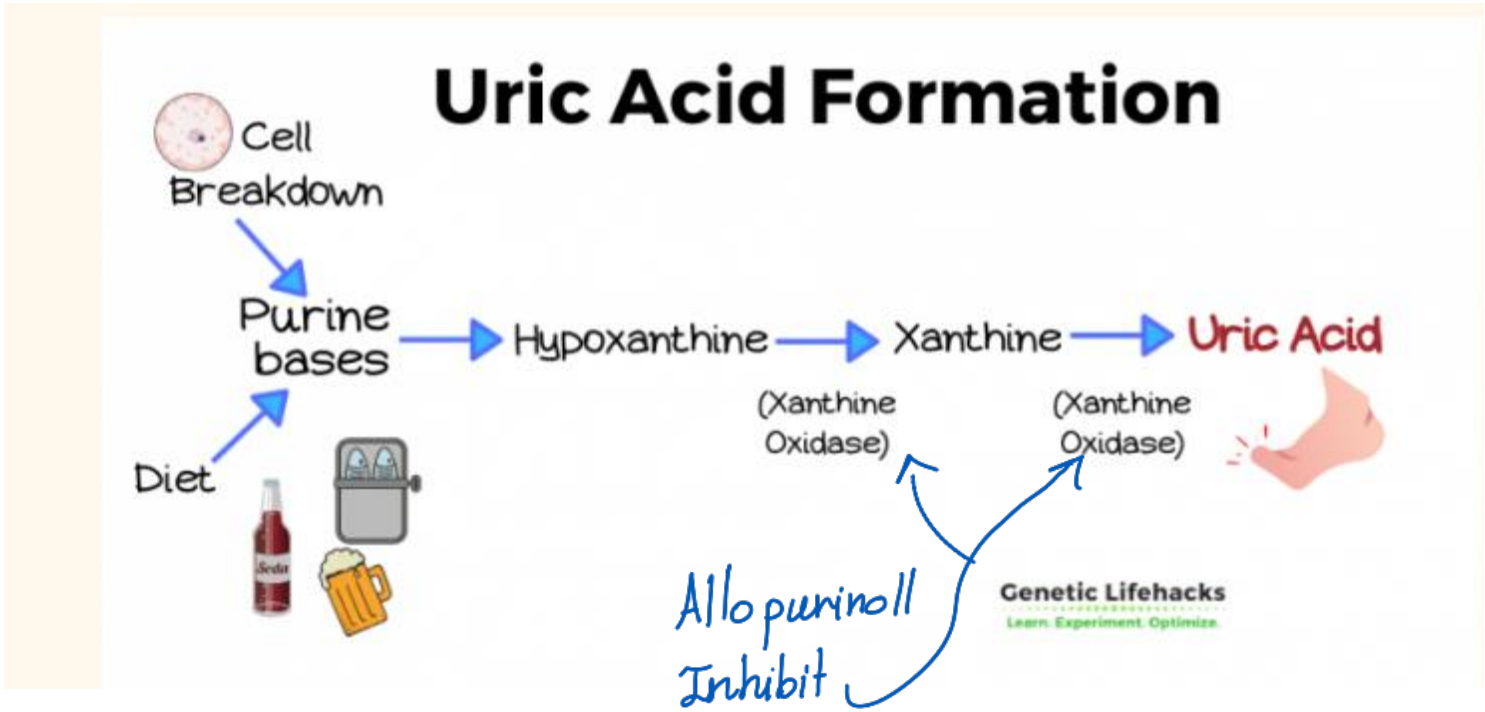
✓ Mechanism of action, toxicities of the different groups of drugs used in the management of gout

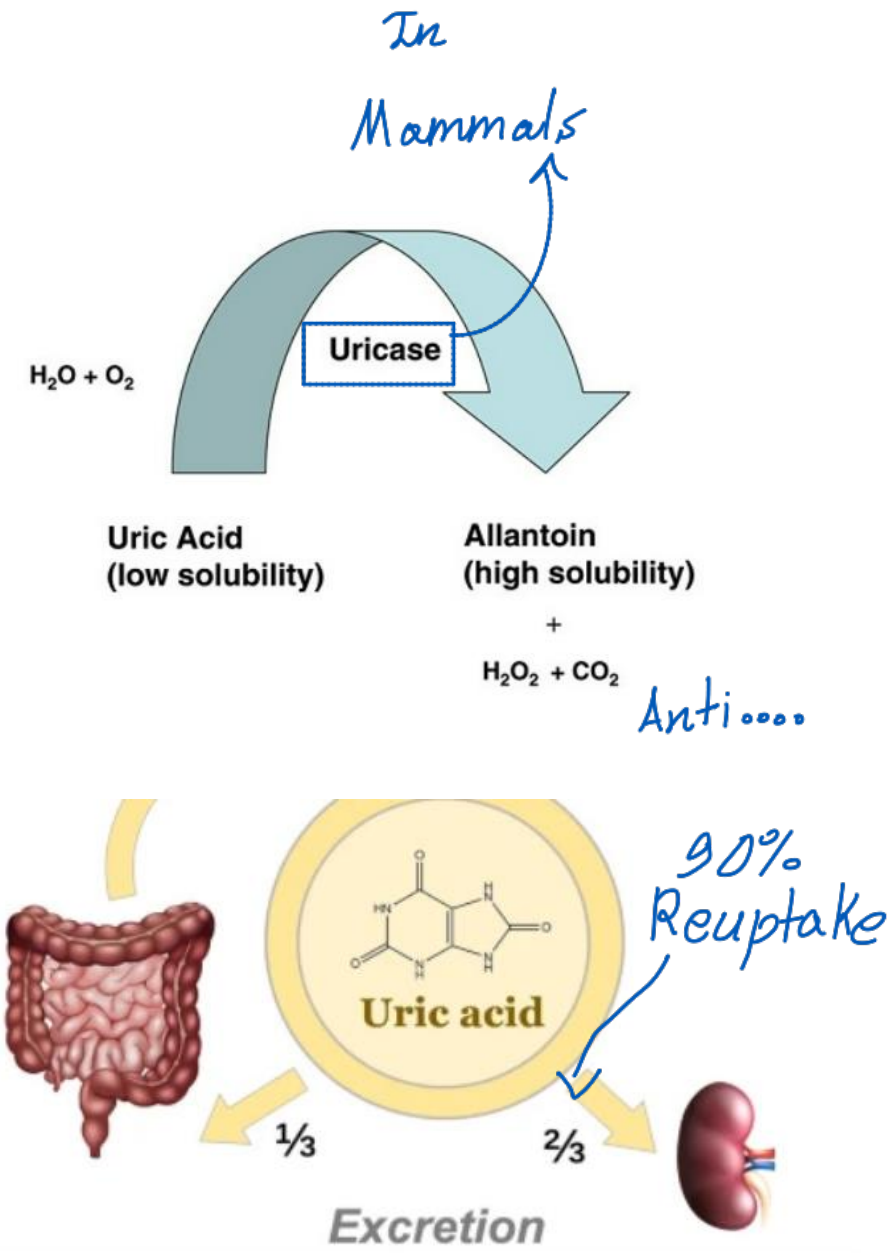
✓ List the drugs that can precipitate gout

What is gout?

G Joint
O mono urate crystalls
U Acute
T Tophi

- Inflammatory arthritis
- Due to monosodium urate crystal deposition in tissues (joints & kidney)
- Presents with acute self-limiting attacks of severe **agonising** pain لا يحتمل الألم
- Chronic – causes **tophi** (masses of uric acid crystals) deposits, joint damage and chronic pain
- **The normal reference range for uric acid is:**
- 1.5 – 6.0 mg/dL for adult women
- 2.5 to 7.0 mg/dL for adult men
- uric acid crystals start to form at **6.8 mg/dL**.


Uric Acid Formation
Cell Breakdown
Purine bases
Hypoxanthine
Xanthine
Uric Acid
(Xanthine Oxidase)
(Xanthine Oxidase)
Diet
Allopurinol Inhibit
Genetic Lifehacks
Learn. Experiment. Optimize.


In Mammals
Uricase
$H_2O + O_2$
Uric Acid
(low solubility)
Allantoin
(high solubility)
+
$H_2O_2 + CO_2$
Anti....
Uric acid
90% Reuptake
1/3
2/3
Excretion

Aetiology

- **1- Overproduction of uric acid: (10%)**
- **Diet**
  - High purine intake: alcohol, fructose, seafood, red meat
- **Increased cell turnover (malignant tumours)**
- Genetic predisposition: **Lesch Nyhan syndrome** x-linked

2- Decreased uric acid excretion (90%) من الحالات

Idiopathic decrease in uric acid excretion 90%

- **Risk factors:**

1 2 3 4 5 6

Males- high purine diet- drugs: thiazide diuretics- diabetes type 2- diet and rapid weight loss- blood cancers

Turn over normally is high in blood cells, so if they were an cancer....

Management of gout

Non-pharmacological

Pharmacological

Non- pharmacological treatment of gout

- **Patients should be educated about**: the importance of lifestyle changes.
- **In overweight patients** - dietary modification to achieve ideal body weight should be recommended
- **Reduction of high purine foods and red meat:**
- liver, kidney and sweetbreads.
- Red meat: Limit serving sizes of beef, lamb and pork.
- Seafood
- Cola beverages- alcohol

Drugs for Treatment of Gout (pharmacological)

- Hyperuricemia does not always lead to gout, but **gout is always preceded by hyperuricemia.**
- **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.

Drugs for treatment of gout

Chronic هدفك تحلل الـ UA في الدم

Hypouricemic drugs

In chronic gout

Uric acid levels> 7 mg/dl

- **1- Increasing uric acid excretion: uricosuric drugs**
- Probenecid
- **2- Decreasing uric acid synthesis allopurinol**: selective inhibitor of the terminal steps in the biosynthesis of uric acid: inhibitor of xanthine oxidase
- **3- Increasing uric acid metabolism uricase enzyme: pegloticase**

"باب"

Anti-inflammatory drugs

In acute attack

- **NSAIDs**
- **Corticosteroids**
- **Colchicine**

Pain subside within 1 hour

Treatment of acute gout

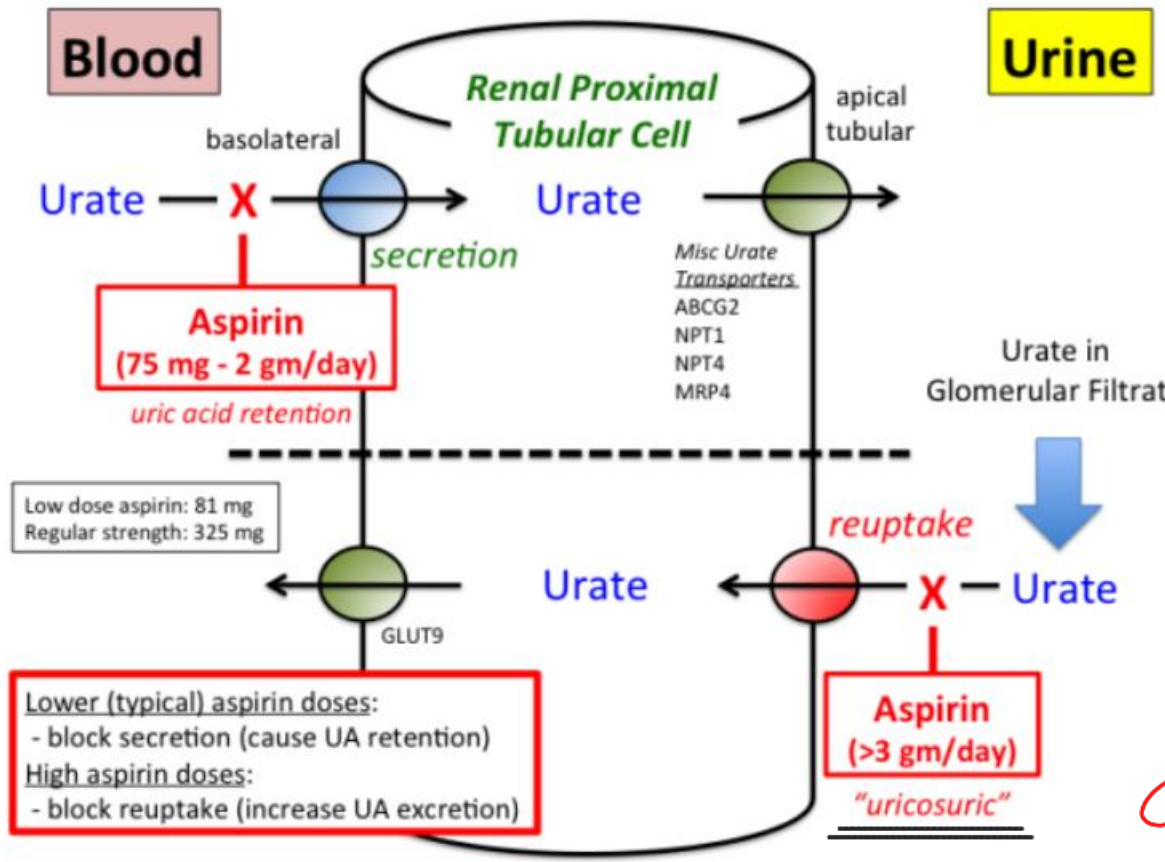
- Acute attacks are treated with **indomethacin**
- **Benefits:**

الأقوى
Most powerful

- 1- Anti-inflammatory: decreasing migration of macrophages into the affected area
- 2- Analgesic: relieving pain.
- NSAIDs other than indomethacin are also effective

- **Note: Aspirin is contraindicated, because it competes with uric acid for the organic acid secretion mechanism in the proximal tubule of the kidney.**

"Organic Acids" هو نفسه Aspirin والـ UA المكان اللي بصير فيه إفراز الـ



Aspirin "81" mg
in small doses
Compete with "UA"
for Excreation Trans
يعني تنزيد كمية الـ UA
وتخلي الوضع أسوء

Aspirin "325" mg or more
in Large doses
Compete with "UA"
for Reuptake Trans
يعني تتقلل كمية الـ UA
وطريقة تحويسة, لكن
في Ad. Effect وسيئة.

Colchicine

مثلة أدوية الشرحان

Unique MOA:

Source:

- Colchicine a plant alkaloid, used for the treatment of acute gouty attacks.
- It is neither a uricosuric nor an analgesic agent, although it relieves pain in acute attacks of gout.

Mechanism of action of colchicine

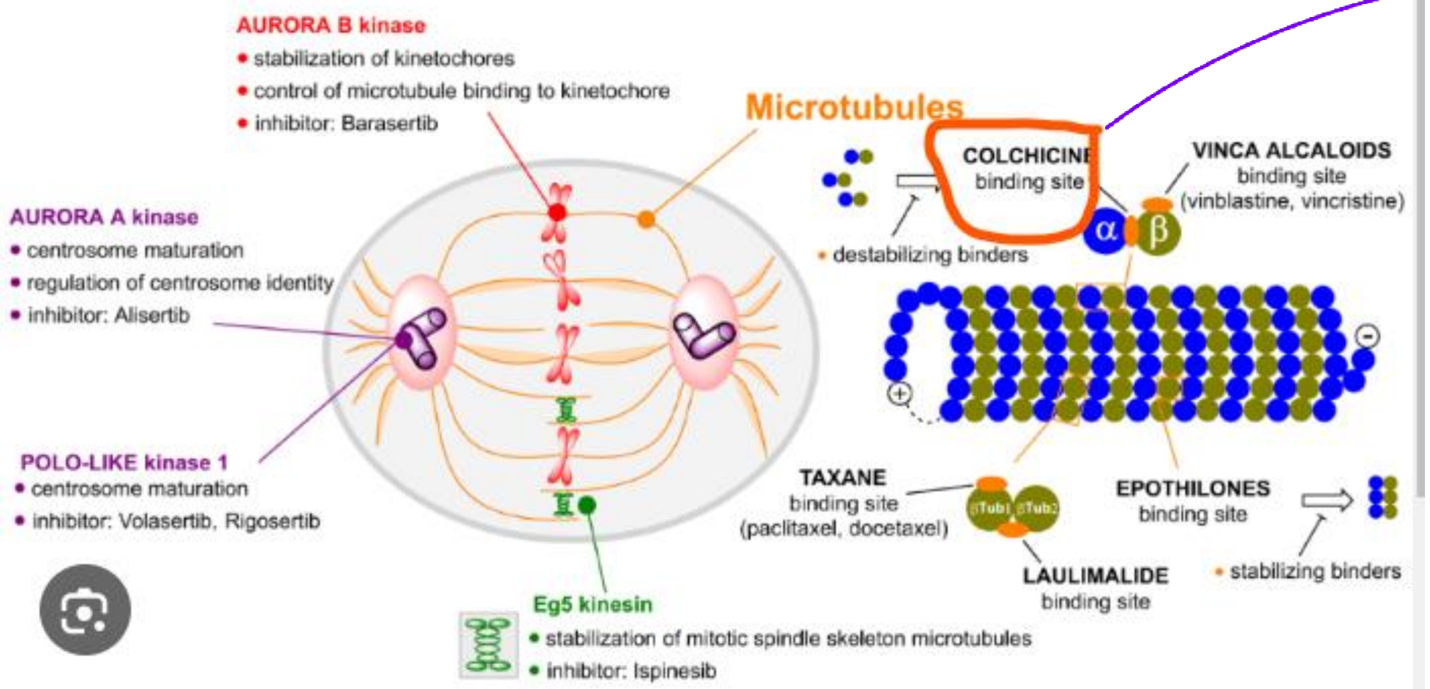
- Colchicine blocks cell division by binding to mitotic spindles (microtubules).

- **Mitotic blocker**: **inhibition of mitotic division in macrophages**: **inhibition of release of cytokines**.
- **Dose**: Colchicine tablet: 0.6 mg One Tablet, after one hour: one tablet, after 12hs: one tablet /12 hs
- **Disadvantages: (2nd choice in acute gouty attacks)**

Until: 1) symptoms subside
2-) Diarhea
3-) Maximum Dose: "7" mg

- 1- Slow onset: alleviates pain within 12 h 2- Sever side effects

- **FAD recommended to stop using colchicine, it is a second choice after corticosteroids and NSAIDs.**



إلي
مكان
خاص فيه

Therapeutic uses of colchicine:

+

- The anti-inflammatory activity of colchicine is **specific for gout**

(Note: Colchicine must be administered within 24 to 48 hours of onset of attack to be effective).

لأنّه شغله بكون
انتهت الميكانيزم تاعت المرض صارت وخلّصت.

Pharmacokinetics:

- Orally, followed by **rapid absorption** from the GI tract.
- Colchicine is excreted **unchanged in the feces or urine**.

Precaution:

Avoided in patients with a creatinine clearance of less than 50 ml/min.

Adverse effects of colchicine:

- **Most common**: nausea, vomiting, abdominal pain, and **diarrhea**.
- **Most rare:** Chronic administration may lead to myopathy, neuropathy and **alopecia.**
- **Most dangerous**: **aplastic anemia**: bone marrow depression 50% mortality

- **PRECAUTIONS**:
- 1- Contraindicated in **pregnancy**
- 2- Should be used with caution in patients **with hepatic, renal, or cardiovascular** disease.
- **The fatal dose has been reported as low as 7 to 10 mg.**

Drugs used for chronic gout /hyperuricemia

Allopurinol:

- Allopurinol is a **purine analogue**
- **Mechanism of action**: It **reduces the production of uric** acid **by competitively inhibiting the last two steps in uric acid biosynthesis that are catalyzed by xanthine oxidase**.

Therapeutic uses: chronic hyperuricemia

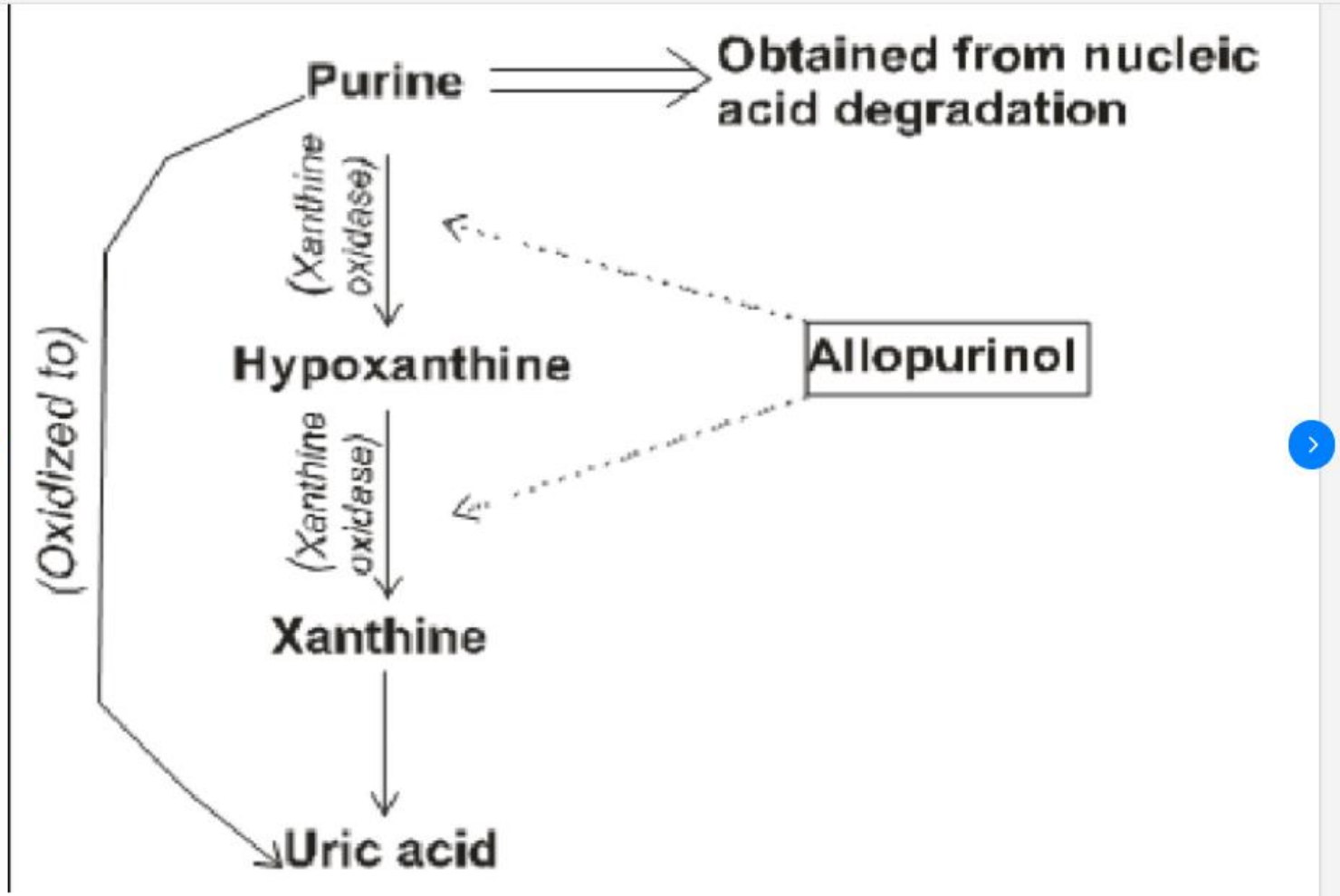
- 1- Primary hyperuricemia of gout (UA excretion)
- 2- Secondary hyperuricemia: tumor lysis syndrome, Lesch-Nyhan syndrome (UA production)
- **Chronic gout**: > 2 attacks of acute gout/ year
- **Dose**: single daily dose: 100mg in the morning

Pharmacokinetics:

- Completely absorbed after oral administration.

- The primary metabolite is **oxipurinol:** t ½ is up to 24 hours; the half-life of allopurinol is 2 hours.

- The drug and its active metabolite are excreted in the feces and urine.



Mechanismof action of allopurinol [7]

Adverse effects of allopurinol:

- Hypersensitivity (skin rash with fever): **may be fatal**: **Stevens-Johnson syndrome (SJS)**
- Headache, drowsiness, nausea, vomiting, diarrhea
- **Precautions:**
- 1- **Acute gouty arthritis**: never use

لأنّه بحرّر بلّم يأخذه من الـ Joint

- 2- **Allopurinol interferes with the metabolism of the anticancer agent** 6-mercaptopurine and the immunosuppressant azathioprine, theophylline requiring a reduction in dosage of these drugs.

لأنّه مستواها بزيد في الدّم

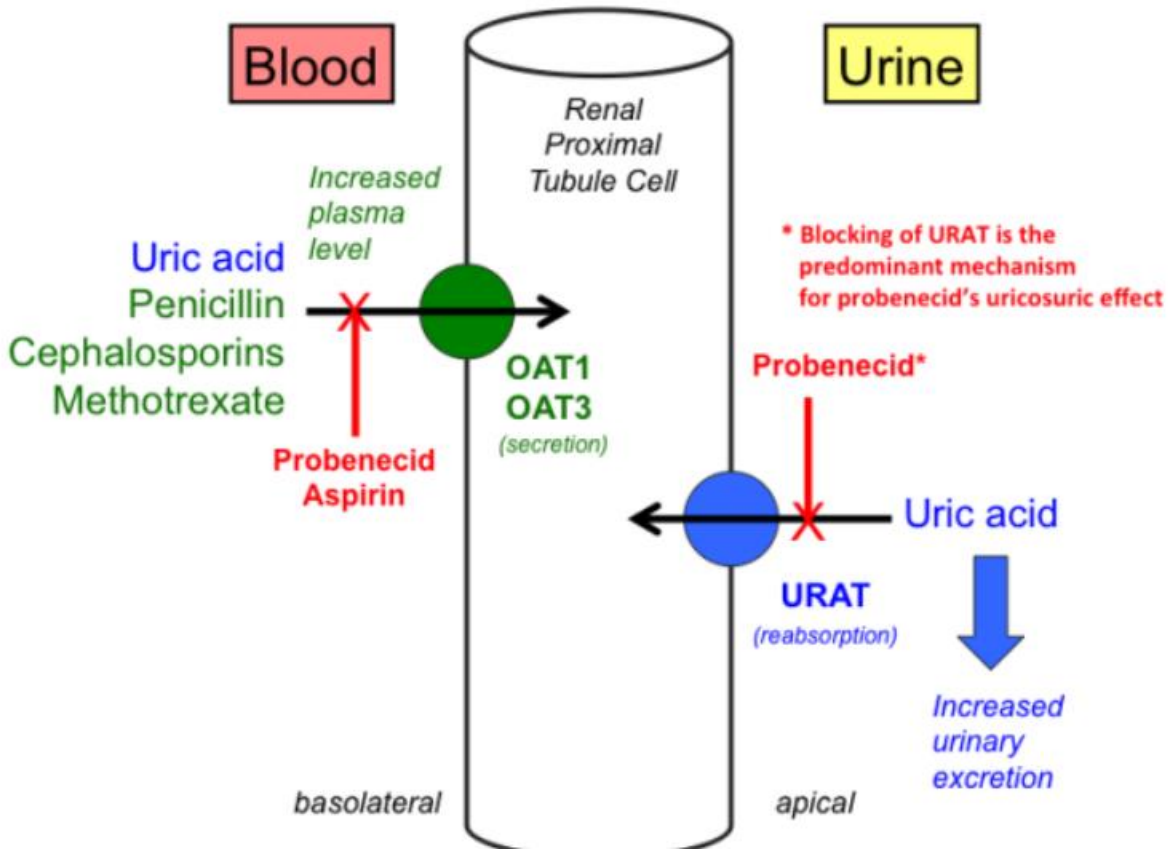
Uricosuric agents:

Probenecid and sulfinpyrazone:

➢ These drugs are **weak organic acids** that promote renal clearance of uric acid by inhibiting the **urate-anion exchanger in the proximal tubule** that mediates urate reabsorption (transporter of reabsorption).

Dose: **high dose**: 0.5 g/day: proben tab. 500mg : 2-3 tab./day

➢ Sulfinpyrazone: a derivative of phenylbutazone


Blood
Urine
Renal
Proximal
Tubule Cell
Increased
plasma
level
Uric acid
Penicillin
Cephalosporins
Methotrexate
Probenecid
Aspirin
OAT1
OAT3
(secretion)
* Blocking of URAT is the
predominant mechanism
for probenecid's uricosuric effect
Probenecid*
Uric acid
URAT
(reabsorption)
Increased
urinary
excretion
basolateral
apical

Adverse effects:

Probenecid and sulfinpyrazone

- Gastric distress
- Probenecid **(small dose):** blocks the tubular secretion (excretion) of penicillin and is sometimes used to increase levels of the antibiotic.

➢Precautions during probenecid therapy:

- **1- Never use in acute attack**
- **2- Increase fluid intake**
- **3- Alkalinization of urine**

Pegloticase

•**Pegloticase** is a **PEGylated enzyme** containing a recombinant form of **mammalian uricase enzyme** derived from a genetically modified strain of E. coli.

•Pegloticase lowers uric acid by **promoting the oxidation of uric acid to allantoin, which is then renally-excreted**.

• Pegloticase was initially approved in the U.S. in 2010.

•**T1/2**: 12 days

•**Dose**: 8mg IVI/2 weeks

•Onset: 24 h

•**Indication**: In chronic gout: sever and complicated cases: sever gouty tophi, gouty nephropathy.

Drugs contraindicated in gout

- These drugs may **precipitate an acute attack of gout by blocking the renal tubular secretion of uric acid,** and raising serum uric acid concentrations.

They include:

- Thiazide and loop diuretics.
- Salicylates and probencid in small dose.
- Acetazolamide.
- Pyrazinamide (antituberculous drug)

References

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Thank you