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).

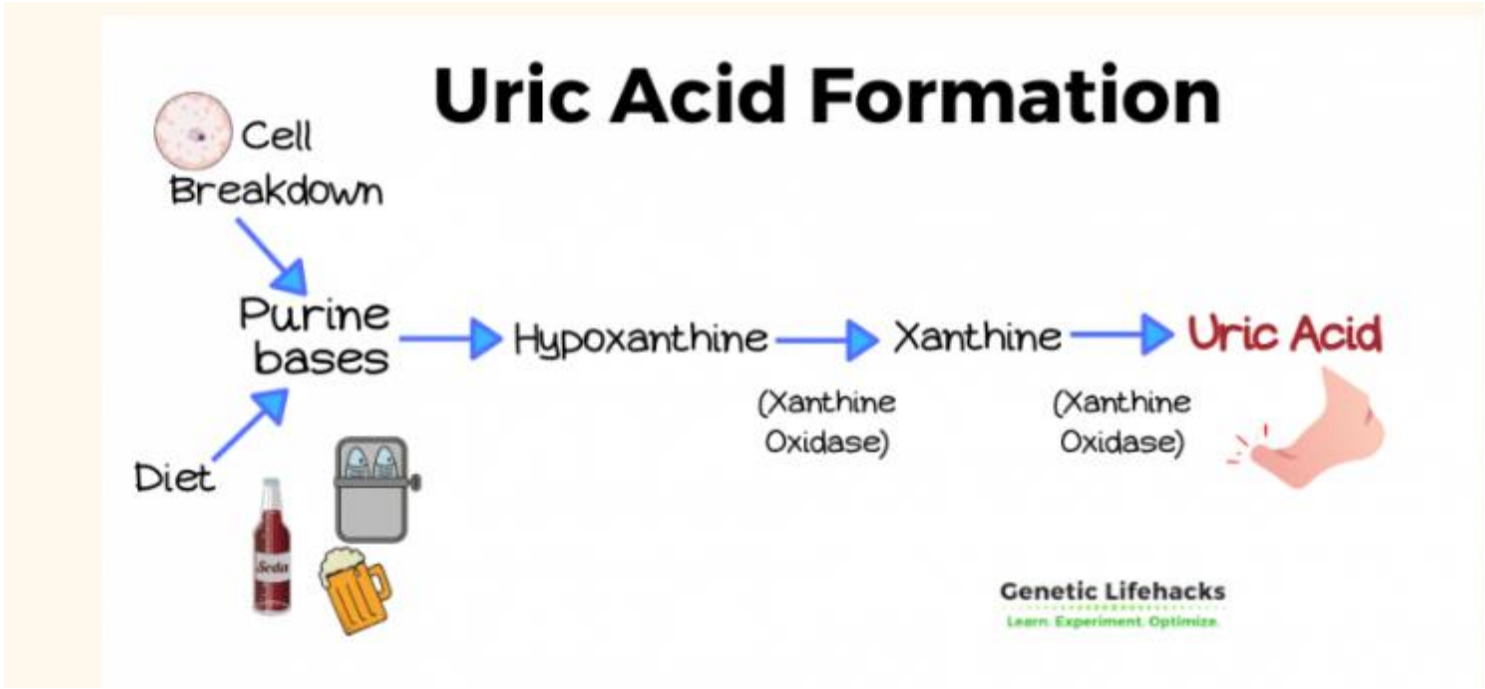
✓ Drugs used for the long-term management of gout (uricosuric agents & allopurinol)

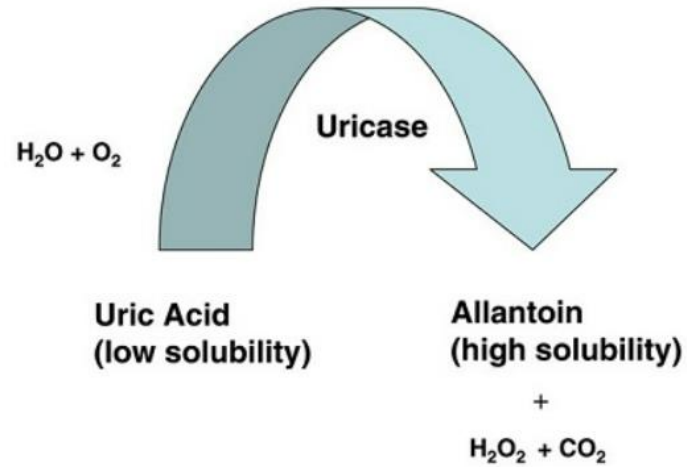
✓ Mechanism of action, toxicities of the different groups of drugs used in the management of gout

✓ List the drugs that can precipitate gout

What is gout?

- Inflammatory arthritis
- Due to monosodium urate crystal deposition in tissues (joints & kidney)
- Presents with acute self-limiting attacks of severe **agonising** pain
- 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 Oxidase)
Xanthine
(Xanthine Oxidase)
Uric Acid
Diet
Genetic Lifehacks
Learn. Experiment. Optimize.


$H_2O + O_2$
Uricase
Uric Acid
(low solubility)
Allantoin
(high solubility)
+
$H_2O_2 + CO_2$


Uric acid
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**

2- Decreased uric acid excretion (90%)

Idiopathic decrease in uric acid excretion 90%

- **Risk factors:**

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

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

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**

Anti-inflammatory drugs

In acute attack

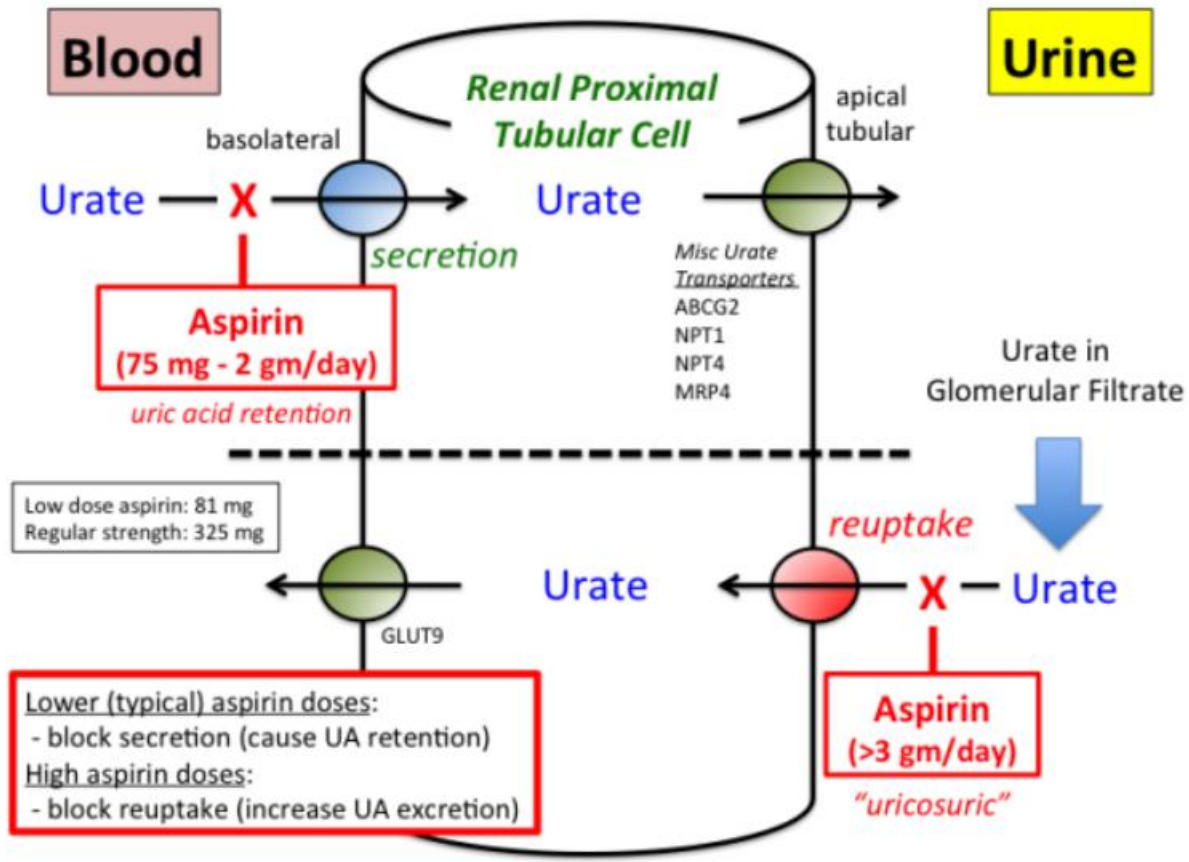
- **NSAIDs**
- **Corticosteroids**
- **Colchicine**

Pain subside within 1 hour

Treatment of acute gout

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


Blood
Urine
Renal Proximal Tubular Cell
basolateral
apical tubular
Urate
X
Urate
secretion
Misc Urate Transporters
ABCG2
NPT1
NPT4
MRP4
Aspirin
(75 mg - 2 gm/day)
uric acid retention
Urate in Glomerular Filtrate
Low dose aspirin: 81 mg
Regular strength: 325 mg
reuptake
Urate
X
Urate
GLUT9
Lower (typical) aspirin doses:
- block secretion (cause UA retention)
High aspirin doses:
- block reuptake (increase UA excretion)
Aspirin
(>3 gm/day)
"uricosuric"

Colchicine

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

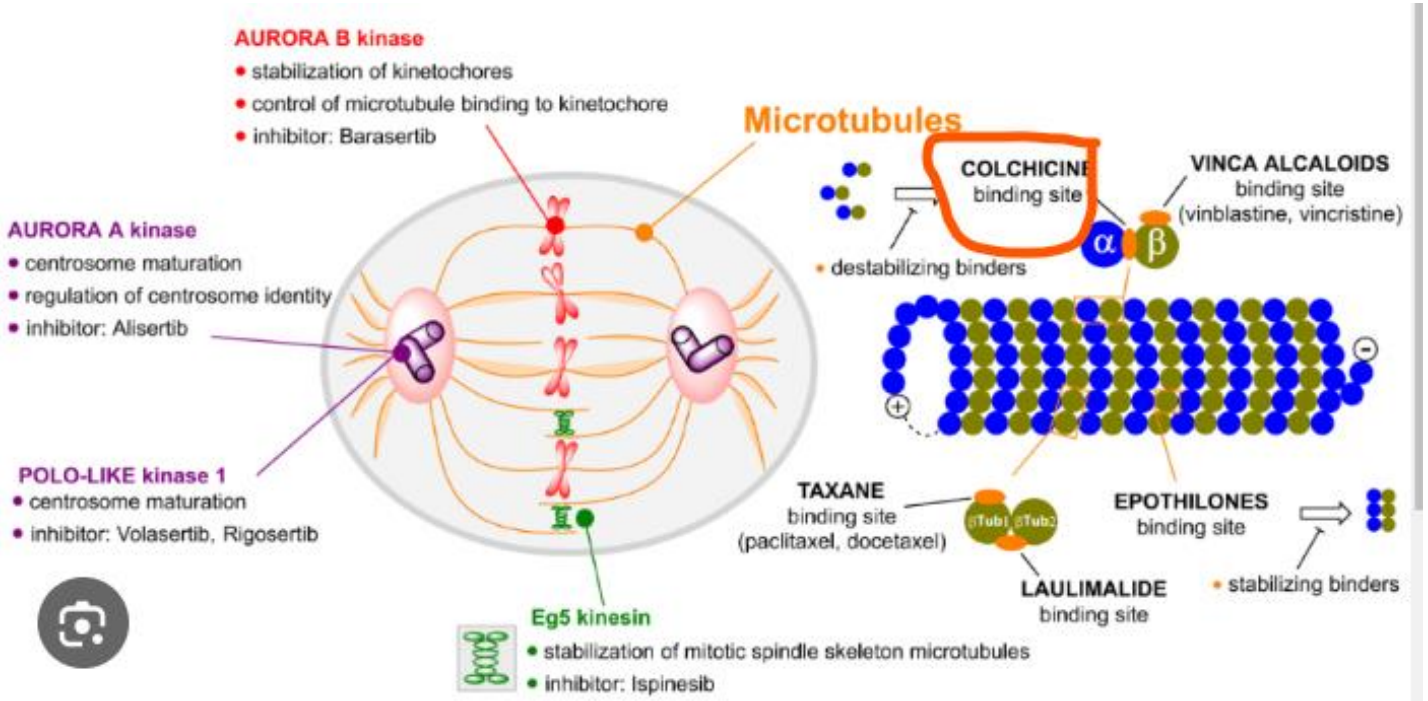
- Colchicine blocks cell division by binding to mitotic spindles (microtubules).

- **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)**

- 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.**


AURORA B kinase
• stabilization of kinetochores
• control of microtubule binding to kinetochore
• inhibitor: Barasertib
Microtubules
COLCHICINE
binding site
VINCA ALCALOIDS
binding site
(vinblastine, vincristine)
α
β
• destabilizing binders
AURORA A kinase
• centrosome maturation
• regulation of centrosome identity
• inhibitor: Alisertib
POLO-LIKE kinase 1
• centrosome maturation
• inhibitor: Volasertib, Rigosertib
TAXANE
binding site
(paclitaxel, docetaxel)
βTub1
βTub2
EPOTHILONES
binding site
LAULIMALIDE
binding site
• stabilizing binders
Eg5 kinesin
• stabilization of mitotic spindle skeleton microtubules
• inhibitor: Ispinesib

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).

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

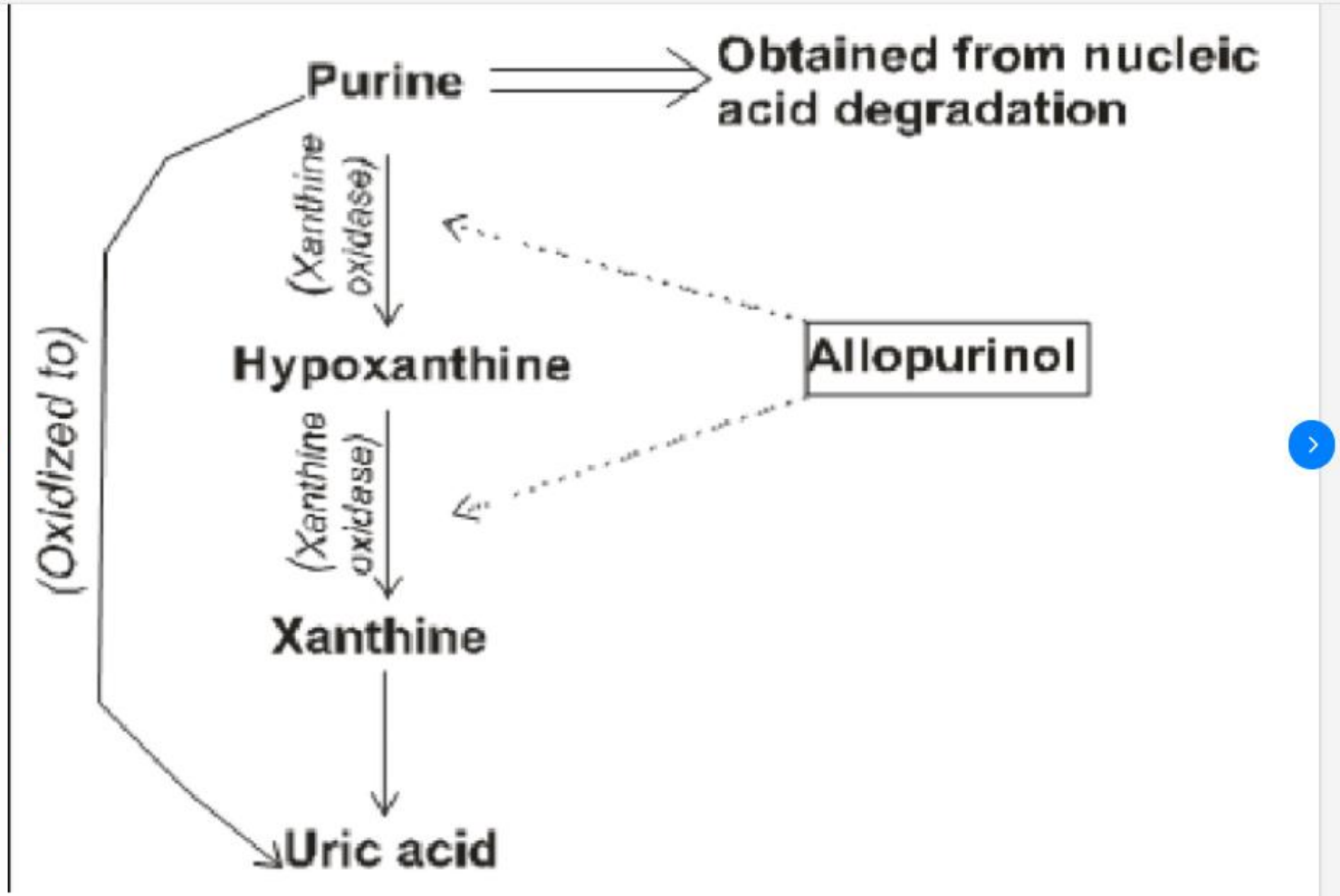
- 1- Primary hyperuricemia of gout (UA excretion)
- 2- Secondary hyperuricemia: tumor lysis syndrome, Lesch-Nyhan syndrome (UA production)
- **Chronic gout**: > 2 attacks of acute gout/ year
- **Dose**: single daily dose: 100mg in the morning

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
- 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.

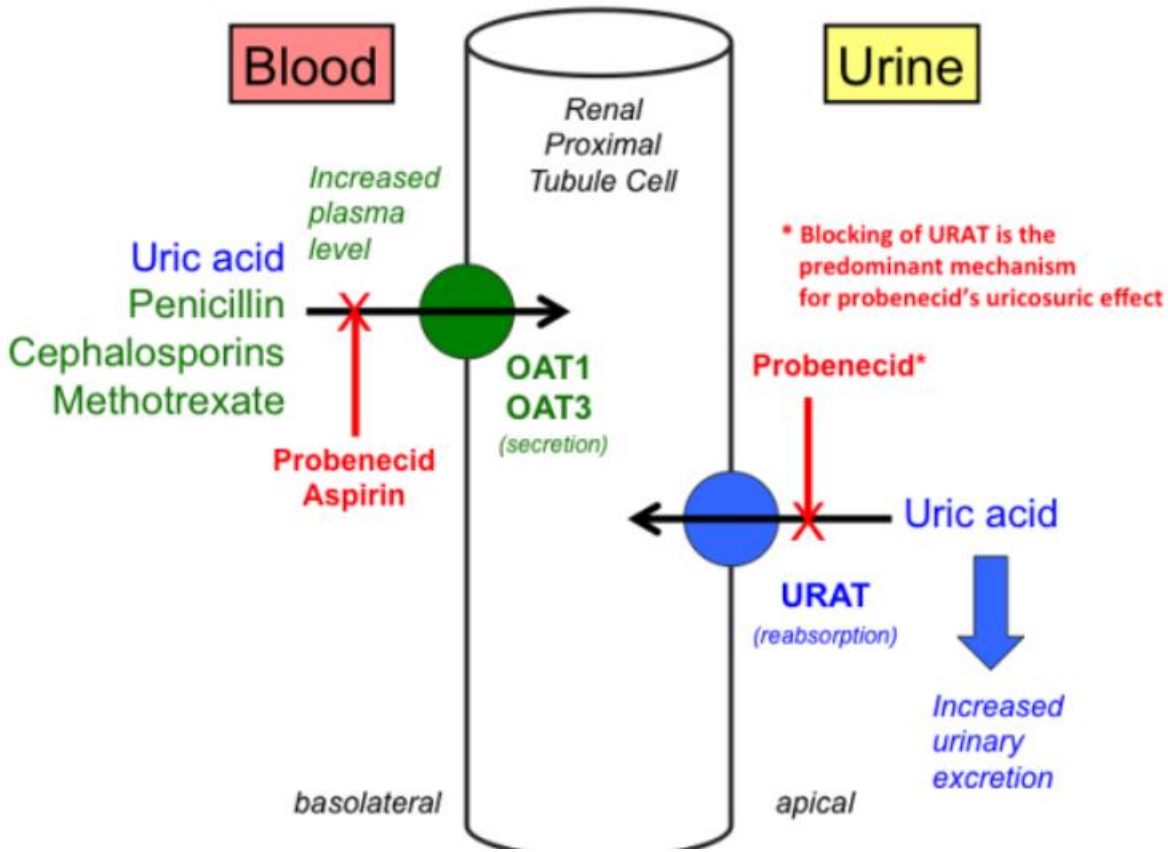
Uricosuric agents:

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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Katzung *by Anthony Trevor, Bertram Katzung, and Susan Masters . 16th edition McGraw Hill,*

Rang & Dale's Pharmacology: *by Humphrey P. Rang ; James M. Ritter ; Rod Flower Churchill Livingstone; 10th edition*

Thank you