Hashemite University
H·U·M
Medical School Committee

Scientific Team
الفريق العلمي

PHARMACOLOGY

Lecture : 2

DONE BY :Hamzeh Al-salhi

Drugs for Gout

-Gout is a metabolic disorder characterized by high levels of uric acid in the blood (hyperuricemia). Hyperuricemia can lead to deposition of sodium urate crystals in tissues, especially the joints and kidney. Simply, it is deposition of uric acid crystals in synovium of joints.
note: if you want to understand the MOA of any drug, go to page 8
-The deposition of urate crystals (as they deposit, they become recognized by the immune system as foreign bodies), initiating an inflammatory process involving the infiltration of granulocytes that phagocytize the urate crystals.

-Imp. Note: hyperuricemia (whatever the level of uric acid) in the bloodstream doesn't necessarily cause gout attacks. Therefore, it is not triggered by a particular level of uric acid but by acute fluctuations.

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

- Gout: Pathophysiology

*As we said, gout is caused primarily by uric acid Deposition.
-The last step of purine synthesis, is the conversion of xanthine into uric acid by the enzyme "xanthine oxidase". So, it is an end product of purine synthesis.

**Uric acid is excreted mainly by the kidney.

**Accordingly, the causes of hyperuricemia in primary gout are:
1) An overproduction of uric acid (rare genetic disorder)
2) And/or the inability to excrete uric acid renally. (in 90% of cases).

- **Pathogenesis**:

-Hyperuricemia leads to precipitation of urate salts (needle-like crystals) in the affected areas. As the immune system recognize these needle-like structure, inflammatory cells start to infiltrate to these structure (mainly neutrophils, as this happens as an acute attack). When neutrophils try to attach to these structures, they will rupture (due to the needle structure), **causing the release of neutrophil's contents of enzyme and cytokines, inducing more and more inflammatory reactions.**

-So, this is the main mechanism of development of **primary gout. (We noticed that there's no any predisposing factor, except hyperuricemia)**

-**Note:** Gout's adaptive immune response (after response of innate immunity response which is mediated by neutrophils and macrophages, as described above) is cell-mediated immune response.

Gout: Causes of Secondary Gout

- Excessive alcohol consumption
- Diet rich in purines
- Nephropathy
- Starvation or dehydration
- Certain drugs

**Each of these has its own mechanism in causing the disease, either in blocking uric acid metabolism (such as alcohol) or anything else.

-Gout is managed in the following 3 stages: Treating the acute attack, providing prophylaxis to prevent acute flares, lowering excess stores of urate (which is the main cause). Sometimes, so patients have a normal uric acid production but have a renal disease. Therefore, we have to understand they pathogenesis of each cause, and according to this we prescribe the drug.

Note: Acute flares of gout usually present as pain, swelling, tenderness, and redness in the affected joints (for example, big toe, knees, ankles, wrists, or elbows).

-So, what are our targets in treatment of either primary or secondary gout?
Most therapeutic strategies for gout involve **lowering the uric acid level below the saturation point (6 mgldl), thus preventing the deposition of urate crystals. This can be accomplished by interfering with uric acid synthesis or increasing uric acid excretion.

Treatment of Acute Gout

Acute gout attacks can result from a number of conditions, including excessive alcohol consumption, a diet rich in purines, and kidney disease. **"We use a combination of drugs, not a single one"

-**NSAIDs**, **corticosteroids**, **anakinra** (IL-1 receptor antagonist) and **colchicine** are effective agents for the management of acute gouty arthritis.

**Very important note: When we should give a prophylactic urea-lowering drugs? Patients are candidates for prophylactic urate-lowering therapy if they have more than two attacks per year or they have chronic kidney disease, kidney stones, or tophi (deposit of urate crystals in the joints, bones, cartilage, or other body structures).

✓ **NSAIDs:** **Indomethacin** is considered the classic NSAID of choice, although all NSAIDs are likely to be effective in decreasing pain and inflammation. **EXCEPT aspirin**, why?

-Because it can inhibit the excretion of **uric acid**, which leads to increased levels of **uric acid** in the body.

So, we use NSAIDs (Indomethacin) in a full dosage for 2-5 days, then we decrease the dose gradually as the symptoms start to subside "Tapering mechanism". **BUT we must continue administering the drug until 2 days after the full subsidence of the symptoms, to make sure that the symptoms have really disappeared.

✓ **Corticosteroids:**

-Intra-articular administration of corticosteroids (when only one or two joints are affected) is also appropriate in the acute setting, or systemic corticosteroids for more widespread joint involvement.

✓ **Colchicine:**

-Colchicine, a plant alkaloid, is used for the treatment of acute gouty attacks.
It is neither a uricosuric (doesn't cause excretion of urea) nor an analgesic agent, although it relieves pain in acute attacks of gout. (so we have to administer NSAIDs with it)

***Very imp.: Colchicine was previously considered as the first choice of treatment, but due to multiple adverse effects and narrow therapeutic index, its use has been largely limited. Therefore, nowadays we use NSAIDs and corticosteroids as the first line of treatment, also anakinra is also useful, but it is very expensive.

- Mechanism of action: Colchicine binds to tubulin, a microtubular protein, causing its depolymerization. **This disrupts cellular functions, such as the mobility of neutrophils, thus decreasing their migration into the inflamed joint**. Furthermore, colchicine blocks cell division by binding to mitotic spindles.

-This mechanism of action has been mentioned before, in anticancer drugs known as (vincristine and vinblastine).

-So, what is the association between this mechanism of action and gout?
We've said that neutrophils are the main inflammatory cells that migrate to the affected region. Neutrophils migrate from bloodstream to surrounding tissues by pseudopodia. **As tubulins are important structural component of microtubules which form pseudopodia, colchicine binds to tubulin and inhibits the formation of pseudopodia, inhibiting phagocytosis process (which requires the action of pseudopodia and inhibiting cell divison. (so it acts in 3 mechanisms to lower the inflammatory response)**

-This mechanism of action is also attributed to it's adverse effects. As this drug inhibits microtubules formation in many body cells, including cardiac cells and many other cells.

- Uses: The anti-inflammatory activity of colchicine is specific for gout, usually alleviating the pain of acute gout within 12 hours. Colchicine is also used as a prophylactic agent to prevent acute attacks of gout in patients initiating urate-lowering therapy. The second use is only traditional use, but nowadays it is only used for acute gouty attacks.

*As we said, Colchicine must be administered within 36 hours of onset of attack to be effective. NSAIDs have largely replaced colchicine in the treatment of acute gouty attacks for safety reasons.

- Pharmacokinetics: Colchicine is administered orally and is rapidly absorbed from the GI tract. Colchicine is metabolized by hepatic CYP450 3A4 and other tissues,excreted unchanged in bile and urine. It undergoes enterohepatic recirculation and exhibits high interpatient variability in the elimination half-life.

- Adverse effects: Colchicine may cause nausea, vomiting, abdominal pain, and diarrhea. Chronic administration may lead to myopathy, neutropenia, aplastic anemia, and alopecia. All these adverse effects are attributed to its effect in destroying important structural elements in various cells and tissues. **The drug should not be used in pregnancy and should be used with caution in patients with hepatic, renal, or cardiovascular disease.**

Treatment of chronic gout

-Urate-lowering therapy for chronic gout aims to reduce the frequency of attacks and complications of gout.

**Here, our target isn't the inflammatory reaction, but it is the underlying cause of the disease which is hyperuricemia.

-Options for treatment include:

- The use of **xanthine oxidase inhibitors** to reduce the synthesis of uric acid.
- Or use of **uricosuric drugs** to increase its excretion, Uricosuric agents (probenecid) may be used in patients who are intolerant to xanthine oxidase inhibitors or fail to achieve adequate response with those agents.

-Xanthine oxidase inhibitors (allopurinol, febuxostaf) are first-line urate-lowering agents. We actually use allopurinol as the first choice, but if hypersensitivity type 4 is high (it is the predominant type of immune response in chronic gout), or the patient isn't responsive. In this case, we switch to other xanthine oxidase inhibitors (such as febuxostaf) or we use uricosuric drugs.

Indications for Uric Acid Lowering Therapy

- American College of Rheumatology Guidelines: “When we consider this patient has chronic gout?”

• Tophus or tophi identified on clinical examination or imaging study (evidence A)
• Frequent (≥2/yr) of acute gouty arthritis (evidence A)
• Chronic kidney disease (CKD) stage ≥2 (evidence C)
• Previous urolithiasis (evidence C)

-For example, if the patient had one gouty attack, he’s surely not a chronic gout patient, he should have frequent attacks of acute gouty arthritis for more than 2 years. Also, urolithiasis (uric acid stones deposited in urinary system) is an indication to start chronic gout treatment.

❖ Allopurinol:

-Allopurinol, a xanthine oxidase inhibitor, is a purine analog.

- 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. (A full diagram that involves all drugs MOA will be involved in the sheet later)

**Allopurinol is completely absorbed after oral administration. The primary metabolite alloxanthine (oxypurinol) is also a xanthine oxidase inhibitor with a half-life of 15 to 18 hours. Thus, effective inhibition of xanthine oxidase can be maintained with once-daily dosing. Excreted in feces and urine.

****Hypersensitivity reactions**, **especially skin rashes, are the most common adverse reactions.**

-Because acute attacks of gout may occur more frequently during the first several months of therapy, colchicine, NSAIDs, or corticosteroids must be administered concurrently (together). Therefore, **we NEVER use allopurinol alone in acute gouty attacks during chronic gout treatment.**

❖ Febuxostat:

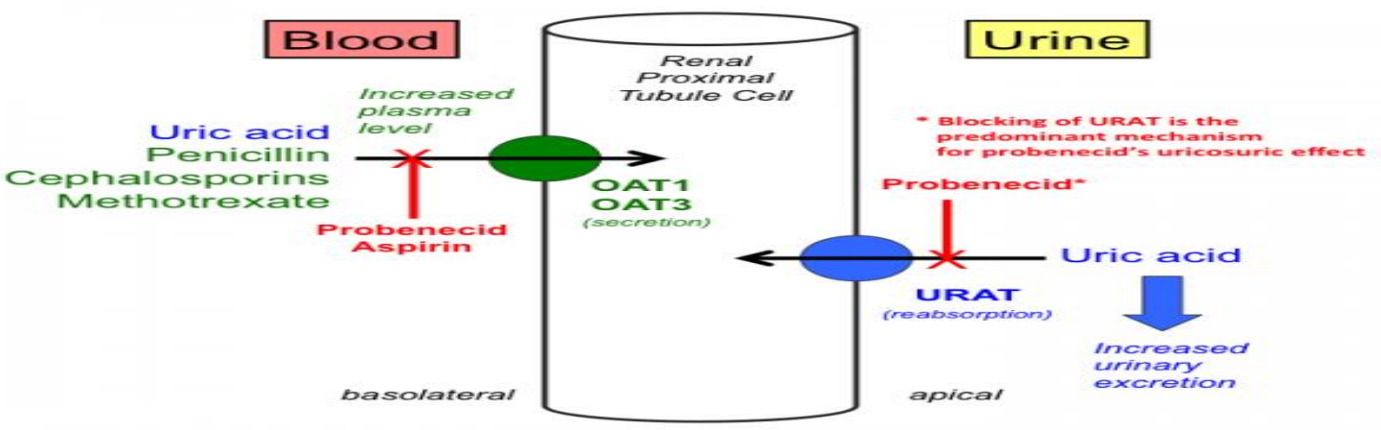
-Febuxostat is an oral xanthine oxidase inhibitor structurally unrelated to allopurinol (non-purine). Its adverse effect profile is similar to that of allopurinol, although the risk for rash and hypersensitivity reactions are greatly lower. So, it is a good choice for patients with allopurinol hypersenseitivity. Febuxostat should be used with caution in patients with a history of heart disease or stroke, as this agent may be associated with a greater risk of these events as compared to allopurinol.

❖ Probenecid:

-Probenecid is an oral uricosuric drug.

❖ Mechanism of action: It is a weak organic acid that promotes renal clearance of uric acid by inhibiting the urate-anion exchanger in the proximal tubule. At therapeutic doses, it blocks proximal tubular reabsorption of uric acid.

**Uric acid is transported to the proximal tubules in order to be excreted in the urine, some amounts of uric acid are reabsorbed back into the bloodstream by 2 transporter protiens, known as (OAT1, OAT3 and URAT4). So, Probenecid inhibits the reabsorption process done by these proteins. Penicillin is excreted by these proteins, so they interfere with the function of probenecid. Thus penicillin is contraindicated with probenecid. (Aspirin also antagonizes the action of probenecid by binding to its target protein).



❖ Peglotlcase:

-Pegloticase is a recombinant form of the enzyme urate oxidase or uricase. It acts by converting uric acid to allantoin, a water-soluble nontoxic metabolite that is excreted primarily by the kidneys. Pegloticase is indicated for patients with gout who fail treatment with standard therapies such as xanthine oxidase inhibitors. It is administered as an IV infusion every 2 weeks.

❖ lesinurad:

- Selective uric acid reabsorption inhibitor (SURI), it inhibits urate transporter URAT1, Inhibits organic anion transporter 4 (OAT4) .So they have the same mechanism as probenecid, but they're more selective than probenecid (we said that probenecid inhibits many transporters and causes accumulation of many drugs). Must be administered with a xanthine oxidase inhibitor.

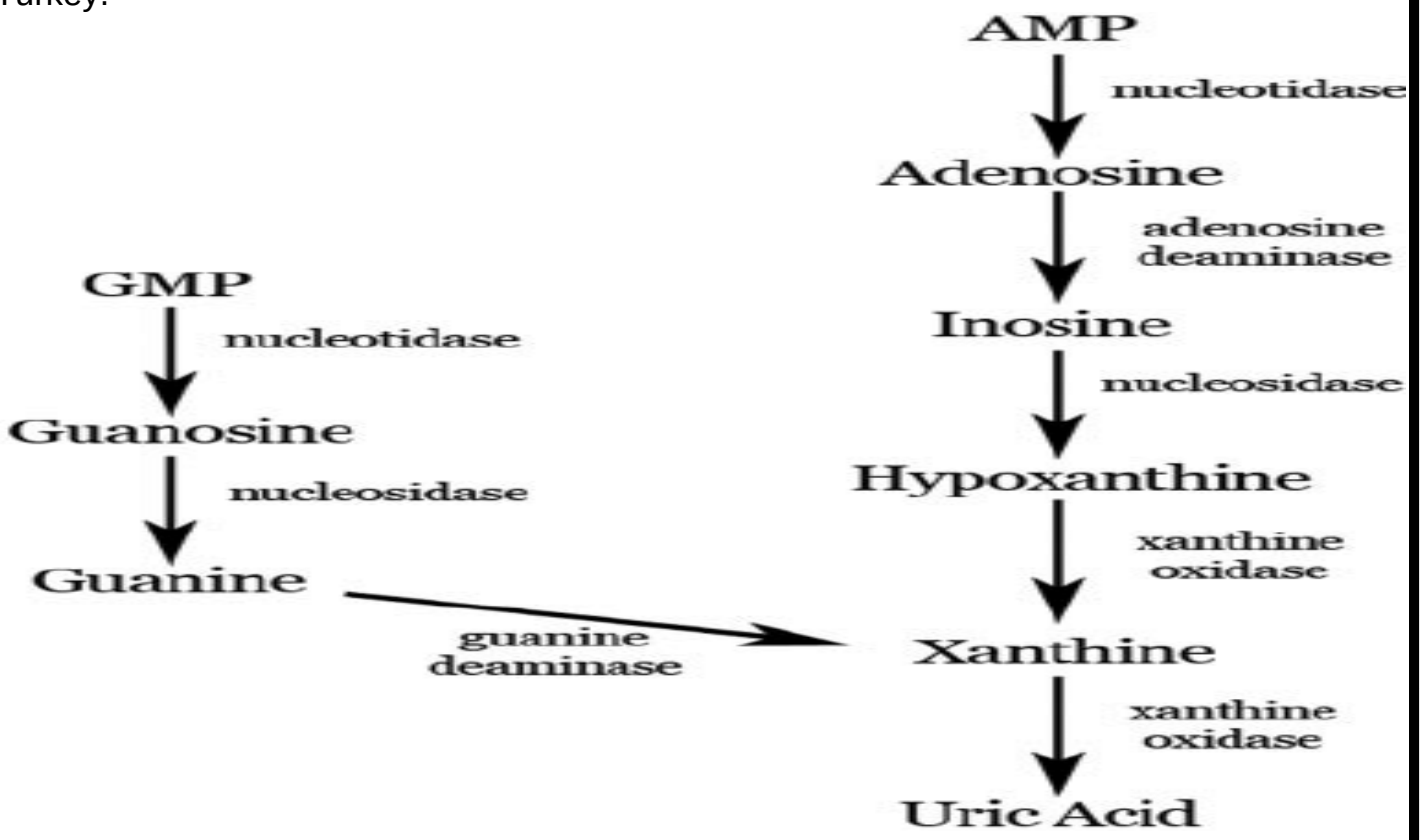
Dietary Restriction

Foods very high in purines:

- Organ meats such as sweetbreads (eg, pancreas and thymus), Smelt, Sardines, Mussels.

Foods moderately high in purines

Trout, Anchovies, Haddock, Scallops, Mutton, Veal, Liver, Bacon, Salmon, Kidneys, Turkey.



We have a separate small topic here.

Acetaminophen

-Acetaminophen, or paracetamol is not considered as NSAID even though it is similar to Ibuprofen.

** Acetaminophen (N-acetyl-p-aminophenol or APAP) inhibits prostaglandin synthesis in the CNS, leading to antipyretic and analgesic effects. Acetaminophen has less effect on cyclooxygenase in peripheral tissues (due to peripheral inactivation), which accounts for its weak anti-inflammatory activity.
**They inhibit PGs synthesis in thermoregulatory regions, causing antipyretic effects, as well as inhibiting PGs synthesis in CNS, which means it is a good analgesic. But it slightly reduces PGs peripherally, leading to weak anti-inflammatory action.

-Acetaminophen is used for the treatment of fever and the relief of pain. It is useful in patients with gastric complaints/risks with NSAIDs and those who do not require the anti-inflammatory action of NSAIDs.

** **Acetaminophen is the analgesic/antipyretic of choice for children with viral infections or chickenpox (due to the risk of Reye syndrome with aspirin).**

➢ Pharmacokinetics:

-Acetaminophen is rapidly absorbed from the GI tract and undergoes significant first-pass metabolism. It is conjugated in the liver to form inactive glucuronidated or sulfated metabolites. A portion of acetaminophen is hydroxylated to form N-acetyl-p-benzoquinoneimine, or NAPQI, a highly reactive metabolite that can react with sulfhydryl groups and cause liver damage. At normal doses of acetaminophen, NAPQI reacts with the sulfhydryl group of glutathione produced by the liver, forming a nontoxic substance. (The drug is safe, unless we take more than 4g a day)

*Acetaminophen and its metabolites are excreted in urine. The drug is also available in intravenous and rectal formulations.

✓ At normal therapeutic doses, acetaminophen has few significant adverse effects. With large doses of acetaminophen, the available glutathione in the liver becomes depleted, and NAPQI reacts with the sulfhydryl groups of hepatic proteins. Hepatic necrosis, a serious and potentially life-threatening condition, can result. Patients with hepatic disease, viral hepatitis, or a history of alcoholism are at higher risk of acetaminophen induced hepatotoxicity.

✓ Acetaminophen should be avoided in patients with severe hepatic impairment.

Study questions

-When a patient is started on an appropriate drug for chronic gout it is observed that that the plasma levels of uric acid decrease while the urine levels of uric acid increase. What drug was the patient treated with?

A. Allopurinol
B. Acetylsalicylic acid
C. Indomethacin
D. Colchicine
E. Probenecid

Answer: E. In chronic gout, the strategy is to decrease uric acid formation from purines by inhibiting xanthine oxidase with allopurinol or increasing urate elimination with uricosurics such as probenecid. Probenecid blocks the tubular reabsorption of uric acid which lowers blood levels of uric acid but results in uricosuria. Colchicine and NSAIDs are less effective and cause more side effects when used in chronic gout. There are preferred In acute gout attacks. Although ASA is uricosuric at anti-inflammatory doses, its toxicity makes the drug a poor choice.

-A 64-year-old man presents with signs and symptoms of an acute gouty flare. Which strategy is the least likely to acutely improve his gout symptoms and pain?

A. Naproxen
B. Colchicine

C. Probenecid
D. Prednisone

Correct answer = C. Probenecid Is a uricosuric agent Indicated to lower serum urate levels to prevent gout attacks. It is not indicated during acute gout flares and should not be started until after the resolution of an acute attack. Naproxen, colchicine, and prednisone all represent viable treatment options that acutely reduce pain and inflammation associated with acute gout attacks.

-In a person who regularly consumes ethanol daily, the potential for hepatotoxicity due to acetaminophen is greater than normal. What is the most likely explanation for this?
A. Cirrhosis of the liver
B. Ethanol inhibits the metabolism of acetaminophen
C. Most beer drinkers are smokers, and nicotine sensitizes the liver to toxins
D. Nutritional deficiency
E. Ethanol induces P450 enzymes that form a toxic metabolite

Answer: E. Ethanol has mixed effects on liver metabolism of drugs.
Acutely, it can act as an enzyme inhibitor, but chronic use may lead to enzyme induction. Acetaminophen is metabolized mainly via conjugation reactions, but a minor pathway involving P-450 (probably the CYP2E1 isoform) results in formation of small amounts of the reactive metabolite, which is (normally) rapidly inactivated by GSH. The chronic ingestion of more than average amounts of ethanol induces the formation of the P-450 isozyme that converts acetaminophen to its reactive metabolite. Thus, more-than-normal amounts of *N*-acetyl-benzoquinoneimine would be formed in an overdose situation, resulting in enhanced hepatotoxicity.

-Best wishes ☺.