Pharmacology

Doctor 2017 | Medicine | JU

Number >>	4
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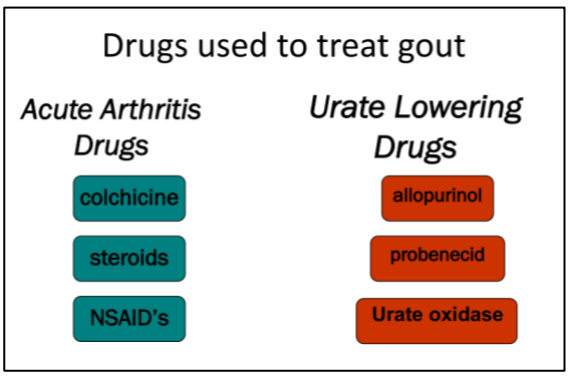
1st system - MSS

This sheet was written based on the lecture that was uploaded on YouTube.

- Some of the slides presented on the right were not elaborated by the doctor, but I have attached them so the sheet can cover all the material.

Last time we talked about gout, and the two types of drugs that are used in gout, which reduce actue arthitis (gout) attack, and other drugs called Urate Lowering Drugs.



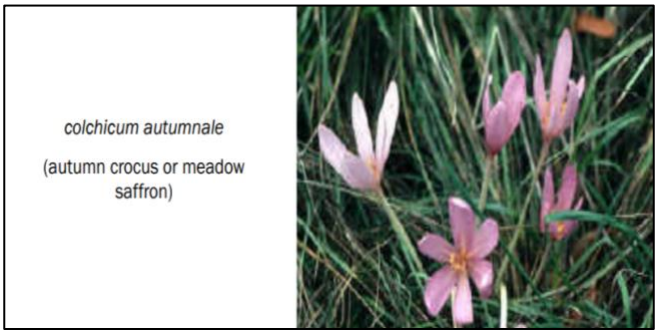
Acute Arthritis

- Include a severe attack, very painful, with acute inflammation and cytokines everywhere (cytokines flare).
- Options: **NSAIDs** (Indomethacin) , if that was contraindicated then you'll use **steroids**(Cortisone), and if both did not work, we then use **Colchicine.**

So the guided way of use is expected to be
NSAIDS → Steroids → Colchicine

Colchicine:

- Herbal derived drug (plant alkaloid)
- Stablizes microtubulin polymerization by binding to tubulin thus stabilizing the movement of the PMNs (polymorphic neutrophils).
- Excretion, exocytosis of cytokines is reduced and the proliferation of the PMNs is also reduced which reduces inflammatory response to deposited crystals.
- Declining use in acute gout (high dose)
- Low dose is still in use for prophylaxis , and to prevent the recurrence of acute gout arthitis attacks. (0.6 mg qd – bid).
- Colchicine is so effective in preventing attacks of familial Mediterranean fever (FMF).



Side effects:

- Not only selective to neutrophils, although most of the drug will bind to neutrophils but since it is taken orally, part of it is going to be excreted in the bile, and then it will undergo re-execretion toward GI tract, and tubulin/splindle depolarization inhibition occurs, which reduces the proliferation of the lining of the epithelial gut, making it unpreferable due to the GI disturbances, which may include infection and diarrhea.

Colchicine adverse effect

- Typical side effects of moderate doses may include gastrointestinal upset, diarrhea, and neutropenia.
- High doses can also damage bone marrow, lead to anemia, and cause hair loss. All of these side effects can result from inhibition of mitosis, which may include neuromuscular toxicity and rhabdomyolysis

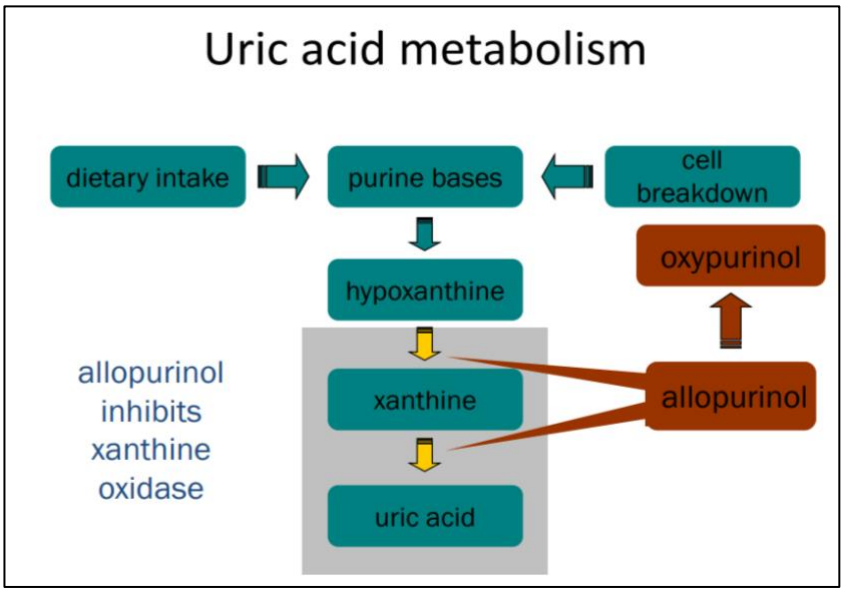
adverse effects dose-related & more common when patient has renal or hepatic disease

- We still didn't solve the problem yet, we only dealt with the signs of crystals formation.

  We need to solve the issue of **Hyperurecemia.**
- We are going to discuss the following drugs: Allopurinol, Probenecid and Uricase.
- We will be talking about Allopurinol, other drugs are not used, and may not be seen.
- There is also a drug called Febuxostat it's an inhibitor of xanthine oxidase and it effectively blocks formation of uric acid. (the doctor said not to focus on this drug).

Allopurinol

- Mainstream in treatment of gout.
- **Inhibits xanthine oxidase.**
- effectively blocks formation of uric acid.



- Hypoxanthine and Xanthine are both very soluble, and wont precipitate to form crystals. (No hyper-xanthinemia and Hyper-Hypoxanthinemia would occur).

We will not witness hyper- xanthinemia because in the normal situation, the serum level of Xanthine + Hypoxanthine is 0.15mg/dl. But with the presence of Allopurinol, it will change to 0.35mg/dl.

The saturation level is greater than 7mg/dl, so we will not face a problem with allopurinol intake.

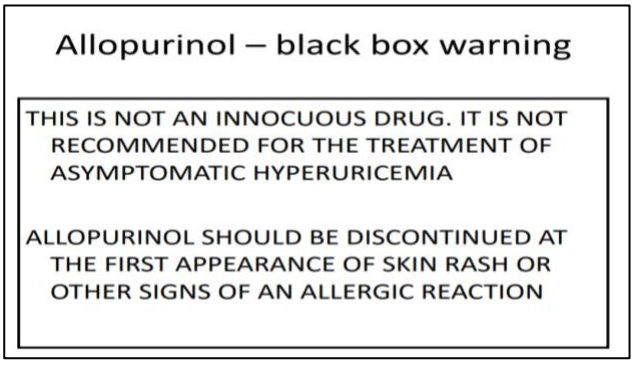
So how do we use Allopurinol?

- Given Once Daily.
- Never use it in Acute Arthritis Gout; during Attack.
- Give it after controlling the inflammation by using NSAID, Colchicine or Steroid for 2-3 weeks then the inflammation should be controlled, and you can give allopurinol while continuing with the NSAID, or Colchicine or Steroid until we reduce the hyperuricemia then we stop the NSAID.
- If the patient has Chronic Arthritis, we give him prophylaxis anti-inflammatory (NSAID, Colchicine or Steroid) along with Allopurinol.
- Lowers Serum and Urine uric acid Levels.

10:00

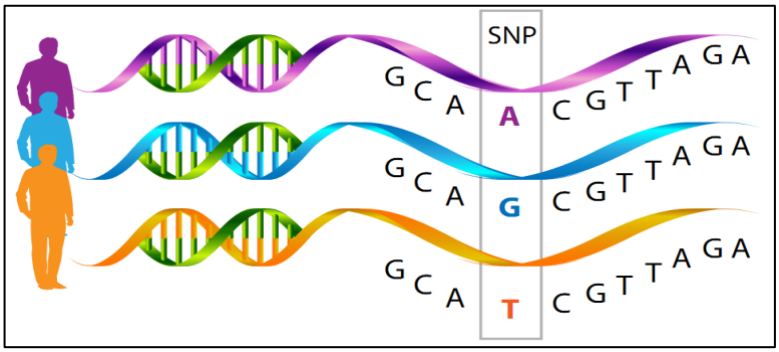
Side Effects

- Very Rare.
- Diarrhea, nausea, abnormal liver tests. And rash which is a rare side effect in Jordan.
- Toxicity.
  We have to do liver tests since Allopurinol affects purines. We need to take care of liver enzymes since it may lead to toxicity, even if it is rare.



- A **black box** warning is the strictest warning put in the labeling of prescription drugs or drug products by the Food and Drug Administration (FDA) when there is reasonable evidence of an association of a serious hazard with the drug. It is basically a warning with a **black box** around it, hence the name.

Pharmacogenetics is the study of inherited genetic differences in drug metabolic pathways (and other pharmacological principles, like enzymes, messengers and receptors) which can affect individual responses to drugs, both in terms of therapeutic effect as well as adverse effects.



SNPs (Single Nucleotide Polymorphisms) in our DNA make us all different, and they are all over the genome which is made up of 3.3 billion nucleotides. 25% of variation in drug response results from SNPs like side effects or non-responses. SNPs might also be responsible for the occurring of different diseases. And may change depending on ethnic variation.

Some other things make patients undergo different side effects; such as their weight, smoking, food, gender.

SNPs might affect the following:

1. **Protein Binding Pocket of the receptor (preventing drug binding to receptor)**

Example: 16% of Jordanians may need higher dose (4 pumps) or just not respond at all to Ventolin (salbutamol) because Amino Acid number 16 Arginine changed into Lysine.

2. **The metabolizing Enzyme**

Metabolizing enzyme got reduced in rate of metabolism of drug, so we will witness toxicity due to buildup of the drug. Or If it was a Pro-drug, it won't be converted into the active form of the drug.

Example: Codeine is a pro-drug, CYP2D6 (which is an isoform of CYP450) converts Codeine to Morphine which is the active form of the drug. 2.5% of the Jordanian population have a SNP in CYP2D6 which would result in a non-active protein (not completed form of the protein) (truncated protein) from the metabolism of codeine thus giving no analgesic effect.

3. **Transportation**
   for example: Mutations in P-glycoprotein will increase the sensitivity and response to drugs, thus increasing the chance of toxicity. Since P-glycoprotein is responsible of pumping the drug outside the cells.
   Another example is the presence of a SNP in the gene encoding for the kidney's transporters (that secrete the drug in the renal tubules) which would result in the transporter not to secrete the drug in the renal tubules.

20:00

HLA are proteins -- or markers -- found on most cells in your body. Your immune system uses these markers to recognize which cells belong in your body and which do not. Thus, responsible for Histocompatibility (before donating an organ from person A to person C we have to check the HLA genes (HLA typing) to check for compatibility between the donor and the recipient), and they are the most frequent genes to undergo mutations which leads to different immunity among people.

What concerns us here is mentioned in the following example:

- SNPs in southeast Asia have **mutation in HLA1805 gene**, which mainly affects the immune system, resulting in recognizing the metabolite of Allopurinol as non-self. Which resulted in an immune reaction which led us to **Steven-Johnson Syndrome (SJS)** and possibly Anaphylaxis afterwards.

SJS: 20% Death rate

Solution: **Genotyping for the patient** -personalized medicine- if he has a SNP in the HLA1805 gene then we don't give him allopurinol and if he doesn't then we give him allopurinol.

- Pill does not fit every patient. Which is the reason why we have the black box.
- If you witness a rash in a patient taking Allopurinol even in Jordan, stop the drug immediately.

- Don't dose patients with kidney failure with Allopurinol.
  Why? Because Allopurinol is excreted by the kidneys so patients with kidney failure will develop build up of drug which will increase the chance of a rash.

Note: we used to say until 2010 that people who have kidney failure shouldn't be given Allopurinol but recently, we give the patient who has kidney failure 1/3 or 1/2 the dose and keep monitoring the patient and if a rash appears on the patient, we then stop the drug immediately.

- Allopurinol is relatively contraindicated with the use of theophylline, 6-Mercaptopurine and Azathioprine.

*6 Mercapto**purine** and Azathioprine* are anti-cancer drugs, which are similar to purine. The cancer cells deal with it as a purine and insert it into its DNA (in DNA replication) which induces chain termination → mitosis stops →Apoptosis

- Azathioprine is a prodrug of 6-Mercaptopurine.

6-Mercapto**purine** → 6-Mercapto**xanthine** → Uric Acid -part of it-

The first metabolism is done by xanthine oxidase. Using a xanthine oxidase inhibitor (Ex: Allopurinol) to inhibit uric acid production will also inhibit the metabolism of 6-mercaptopurine, which therefore will increase blood plasma concentrations of these drugs, and therefore their effect and toxicity.

- **Solution:** we lower the dose of 6-Mercaptopurine/Azathioprine to 1/3 To compensate the decrease of its metabolism by Allopurinol.

- In the case of cancer, we use Allopurinol without the presence of gout due to the presence of Tumor Lysis Syndrome. When you give an Anti-Cancer drug in a high dose to kill cells, there will be a flare of nucleotides → higher purine metabolism→uric acid concentration will increase in the blood leading to increased kidney secretion of uric acid that eventually the kidneys can't handle it leading to kidney stones -kidney toxicity- forming → Tumor Lysis Syndrome.

Solution: give Allopurinol to decrease uric acid secretion. & If the cancer patient was also taking 6-mercaptopurine, again: we decrease it to 1/3.

Result: Allopurinol is RELATIVELY contraindicated with concomitant use of 6-mercaptopurine

Note: Azathioprine is a prodrug for 6-mercaptopurine, used for many diseases including Autoimmune diseases.

Theophylline:

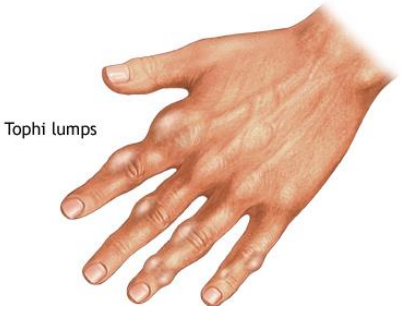
- Is basically Xanthine (metabolized by xanthine oxidase).
- Narrow Therapeutic index drug.
- Never use Theophylline with Allopurinol.
- Although 6-mercaptopurine and Azathioprine aren't wide therapeutic index drugs, but they are not as narrow as Theophylline.
- Additional information: when you want to give Examples on narrow therapeutic drugs, we say digoxin first then warfarin then theophylline.
- That is why Theophylline is NOT susceptible to dose-lowering ideas. NEVER USE IT.
- Used for Asthma.

30:00

up until here we discussed Allopurinol

Urate Oxidase

A patient came up to you with excessive pain and appeared to have tophi which is a spherical deposit of crystalline uric acid and other substances at the surface of joints or in skin or cartilage in people with longstanding hyperuricemia (high levels of **uric acid** in the blood), **Tophi** are pathognomonic for the disease **gout**. Allopurinol won't give a positive outcome (Tophi won't dissolve).



- We should **use Uricase**: An enzyme that destroys Uric Acid.
- We surely lack uricase in our body which is why we have this issue in the first place; we obtain it from some mammalians, e.g. pigs. And then give it to humans, it produces an allergic reaction.

Solution for the resulting allergic reaction: Recombinant DNA production.

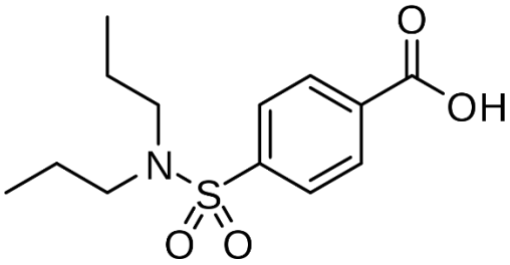
- **Recombinant DNA:** We insert the gene to an E.coli then we colonize it , after that we insert it on the yeast and produce this protein "Rasburicase" (-Dr.Malik said that, I don't understand what the yeast's role in this process too)

Recombinant DNA technology, joining together of **DNA** molecules from two different species that are inserted into a host organism to **produce** new genetic combinations that are of value to science, medicine, agriculture, and industry. (I got this from the web)

- **Rasburicase** was produced to prevent uric acid accumulation rather than using Allopurinol.
- Rasburicase is used in acute hyperuricemia in patients receiving chemotherapy.
- It is not approved for gout.

- **Egloticase** (PEGylated form of urate oxidase) was FDA approved in 2010 for the treatment of chronic gout in adult patient's refractory (unresponsive) to "conventional therapy" of gout.
- PEG: Polyethylene Glycol, reduces solubility, extending its half-life.
- Urate oxidase is a protein so we can't take it orally because of the stomach acidity. This makes injection is the only way to take it.
- It is not convenient for the patient to take injections daily so, we use PEGylated forms of it to decrease the frequency of giving the drug to one time every one or two weeks.
- NOT found in Jordan.

Uricosuric Therapy Probenecid



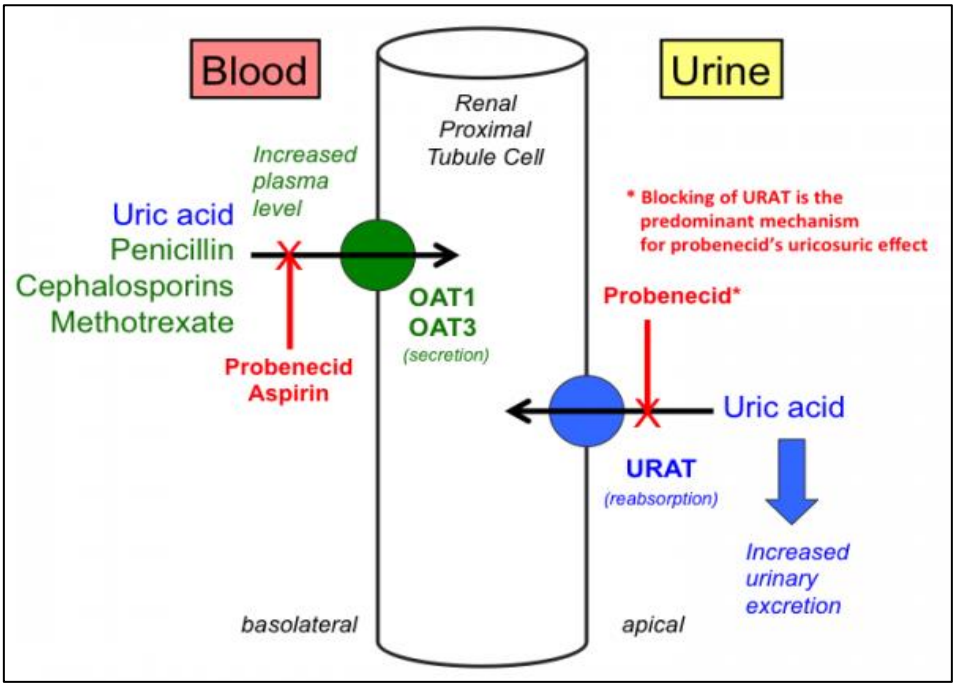
- Blocks tubular reabsorption of uric acid
- Enhances urine uric acid excretion (Good)
- Increases urine uric acid level (Bad)
- Decreases serum uric acid level (Good)
  - What makes it different from Allopurinol is that allopurinol decreases both serum and urine level which is very good, and does not increase kidney stones, and kidney toxicity.
  - **Probenecid** may produce lithiasis.
  - When uric acid reaches the bowman's capsule for filtration, it won't be excreted in urine. Our body will try to get rid of the uric acid through Organic

Anion Transporters which are found between the blood and the nephron. Secretion will take place from blood to renal proximal tubule and so it will enter filtrate (urine), after a while it will pass through another transporter called URAT1 which reabsorbs uric acid that was secreted. And serum level of uric acid increases.

Note: Secretion → from blood to kidney's proximal tubule.

- **Probenecid inhibits the reabsorption of uric acid (2nd step)**

Which explains why urine uric level increases.



- We mentioned in the first lectures that our problem is excretion and not production
- BUT this only decreases ≤ 10% of uric acid level in blood

Result:

- Probenecid is not very effective ALONE in lowering uric acid.
- If allopurinol was not very effective, we add probenecid.

Side effects of Probenecid:

- Moderately effective.
- increases risk of nephrolithiasis (lithiasis means stones).
- not used in patients with renal disease (because it produces renal stones).

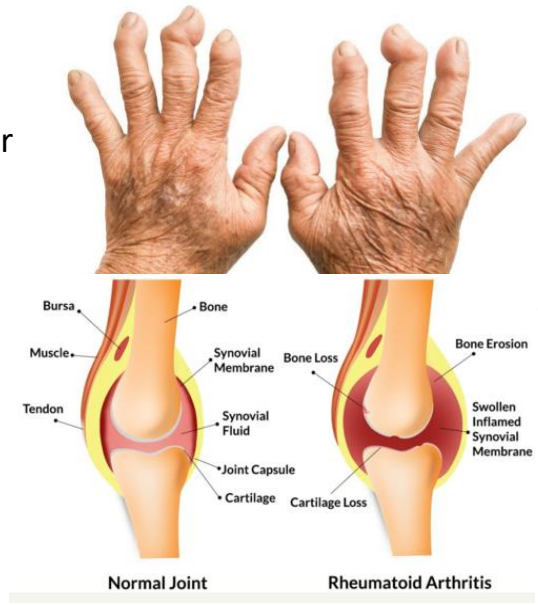
- frequent, but mild, side effects

40:00

- some drugs reduce efficacy (e.g., aspirin) – use any NSAIDs in gout except Aspirin-.
- During the first excretion reaction there is a competitive inhibition between aspirin and uric acid, which leads to inhibition of excretion of uric acid, this results in higher uric acid level in blood (that's why aspirin is contraindicated in Gout).
- Since excretion is inhibited/decreased, then reabsorption inhibition is inhibited/decreased as well; and therefore, reducing probenecid efficacy.
- Aspirin: Drug-to-Drug interaction with Probenecid.

up until here we have discussed GOUT

Rheumatoid Arthritis



- Another name for rheumatism
- An Autoimmune disease.
- Autoimmune disease: a condition in which your immune system mistakenly attacks your body for a foreign antigen; self-destruction.
- There are proteins that are producing antibodies in the small joints in symmetry (like on the two legs for example and not just one leg).
- Proteins are being disposed in joints area followed by an immune reaction which is mostly inflammatory attack on the bone causing deformity.
- We need to act fast and aggressively to prevent deformity.

  How do we check if a patient has rheumatoid arthritis?

  By putting the patient through a Rheumatoid Factor (RF) test if it turns out positive then he has rheumatoid arthritis (we also do other tests, but this is the most important one).

Solution: high dose of NSAIDs to stop immune system reaction.

If it didn't work, Glucocorticosteroids.

- We don't use colchicine because we don't have phagocytosis and PMNs.
- We stop inflammation and therefore, we prevent deformities.
- Along with it, we give DMARDs (Disease-modifying anti-rheumatic drugs), they need months to work (1.5-2).
- We proceed on using (NSAIDs or Glucocorticosteroids) along with DMARDs

  This is called bridging therapy
- When we reached a limit where they don't work anymore, we drop out NSAIDs and continue to treat the symptoms, not the disease.

Best of Luck.