Pharmacology

Doctor 2017 | Medicine | JU

Number >>	3
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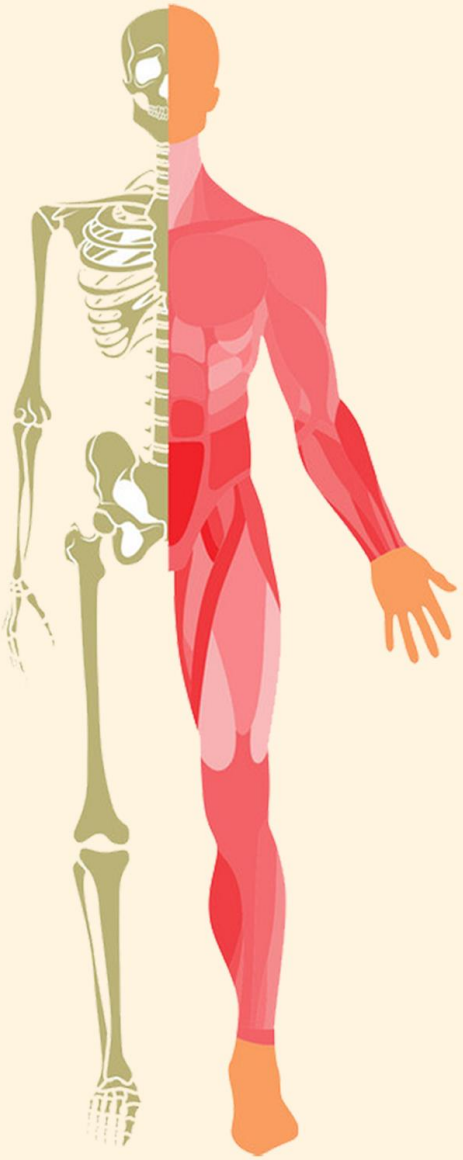


1st system - MSS

Meloxicam

- **Only preferentially** (rather than highly) **selective to COX 2**, particularly at its lowest therapeutic dose of 7.5 mg/d, therefore:
    1. *Meloxicam* **does not have GI toxicity** (because of its higher COX-2 selectivity).
    2. *Meloxicam* **does not have cardiotoxicity** like the other selective COX 2 inhibitors, because its COX 2 selectivity is still relatively low.
    3. But *meloxicam* still **has toxicity on nephron** ($\rightarrow$ small constriction on efferent arteriole and renal failure in chronic use) and **can oppose hypertension drugs**.

    Yet meloxicam is still preferred to other drugs because of its reduced GI adverse effects and because its relatively higher COX 2 selectivity.

- Has **good anti-inflammatory** effects due to its **long half-life** (**>24 hrs**) and is taken only **once daily**.
- The drug has been approved for the treatment of osteoarthritis and rheumatoid arthritis.
- It is associated with fewer clinical GI symptoms and complications than *piroxicam*, *diclofenac*, and *naproxen*.
- Expensive

Coxibs: all Coxibs are **selective COX-2 inhibitors** (ex. *Deracoxib*, *Celecoxib*, and *Valdecoxib* [VIOX]), therefore they have no GI adverse effects and are used in patients with peptic ulcers. However, as we mentioned in previous lectures, they **have high cardiotoxicity and cause thrombosis** in blood vessels and are thus contraindicated in patients who have a history of MI (Myocardia Infarction), angina pectoris, or those who have stents. Also, like many anti-inflammatory drugs they **have renal toxicity**.

Viox used to be a very popular drug but was later withdrawn because of its SEVERE cardiotoxicity.

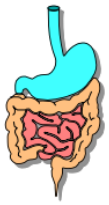
***The higher the COX 2 selectivity, the higher the cardiotoxicity.**

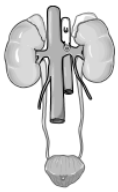
FINAL NOTE ON NSAIDs:

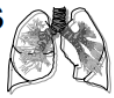
Delay/prolongation of labor connected with PGF2α inhibition. PGF2α is needed in labor, therefore don't think of using NSAIDs in labor analgesia, because labor pain is too severe, and the drug will have no efficiency.

Shared toxicities of NSAIDs due to prostanoid synthesis inhibition

1. **Gastric mucosal damage**
   connected with PGE inhibition
2. **Bleeding:** inhibition of platelet function (TxA_2 synthesis)
3. **Limitation of renal blood flow**
   Na^+ and water retention
4. **Delay / prolongation of labour**
   connected with $PGF_{2\alpha}$ inhibition
5. **Asthma and anaphylactoid reactions**
   connected with $PGF_{2\alpha}$ inhibition







**The Dr only mentioned no.4 in this lecture, but have a look at the rest because the Dr said the source for his test will be both his lecture + slides.*

Gout (النقرص)

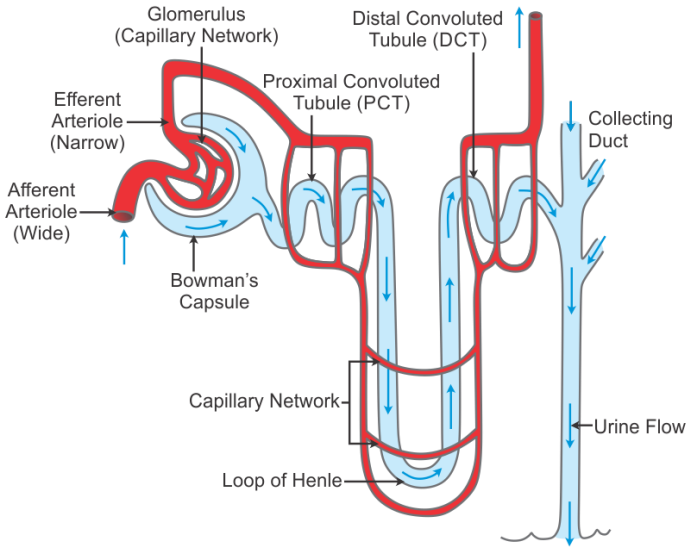
Gout is becoming a very common problem especially in the middle east and is **caused by hyperuricemia**. About 1% of the population have hyperuricemia (not gout) making it a common condition. Not everyone who has hyperuricemia develops gout, but hyperuricemia is the biochemical description of preliminary gout. It's a common misconception that hyperuricemia is caused by overconsumption of protein red meat, and although it is a risk factor, **only 10% of hyperuricemia cases are caused by red meat overconsumption. Rather, the most common cause of hyperuricemia is hypo excretion of uric acid.**

Uric acid is produced from purines (*reflect on biochemistry 2 last semester*). Sources of purines are dietary intake or cell breakdown (can be increased drastically when using anti-cancerous drugs → cell lysis syndrome). Purines are transformed into *hypoxanthine* which is then oxidized into *xanthine* and oxidized again to *uric acid*. **The 2 oxidation rxns are catalyzed by *xanthine oxidase*.**

Uric acid buildup is a problem because it **is not very soluble in the blood, which causes it to crystalize. Urate crystals in joints cause gout by inflammation. Hypoxanthine and xanthine are both about twice as soluble as uric acid so** there's no issue if those molecules build up in the blood instead of uric acid because **they won't crystalize**, and indeed, this is what some medications aim for.

When there are elevated levels of uric acid in the blood, the body in turn needs to amp up the level excretion by the kidney into the urine, let's have a look at the mechanism:

1. First of all, since uric acid is soluble (to a limited degree) in the blood, it cannot be 'filtered' through the glomerulus into Bowman's capsule. Instead, uric acid is ***secreted*** directly from the blood into the proximal tubule through the '***organic anion transporter***'.
2. Next, about 90% of the uric acid is reabsorbed back into the blood, leaving behind about 10% to be **excreted**.



Uric acid is reabsorbed because it is actually needed in circulation but in controlled amounts, therefore, the amount (not percentage) of uric acid excreted is increased in proportion to the elevated amount found in the blood. So how is hyperuricemia caused? Either by:

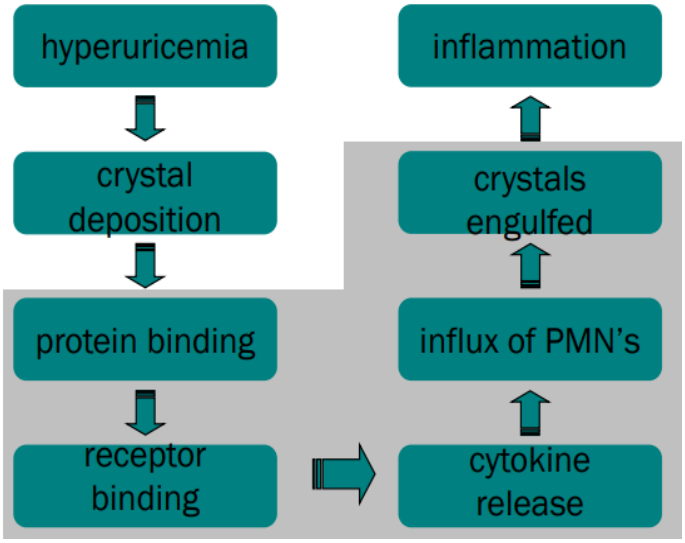
1. High dietary intake,
2. Overproduction of uric acid (cell lysis syndrome with anti-cancerous drugs), or by
3. **Under-excretion** of uric acid, and this usually occurs **by competitive inhibition of weak-acid** drugs like ASPIRIN or *thiazide* diuretics **with uric acid** on the secretion activity of the '**organic anion transporter**', therefore uric acid builds up in the blood. THIS IS THE MAJOR CAUSE OF HYPERURECEMIA AND GOUT.

Hyperuricemia Classification	1. Overproduction	2. Under-Excretion
Serum level	High	High
Urine level	High	Normal/Low

Crystal induced inflammation - Steps:

- As we said previously, uric acid is not very soluble and will crystalize in regions with slow blood flow like in synovial joints.
- When these **crystals are deposited in the joint cavity**, the immune system recognizes them as foreign bodies from their antigenic proteins.

- The immune system knows that the crystals shouldn't be there so signals are sent to start an inflammatory rxn in the joint by way of **cytokines** (ex. TNF-α, ILs, PGs, TXs) to eliminate the crystals.
  Note: this is the process in which **chronic** (not acute) gout occurs little by little, pain only starts after prolonged activity and only in joints experiencing a lot of pressure like in the big toe. Pain is severe. Inflammation is weak/moderate. The next steps highlight the main events of what happens during an **acute gout attack** ↓…



- As we know by now, the first responders to the signals would be **PMNs** (Poly MorphoNuclear leukocytes), which **arrive at the site and some start to engulf the crystals**. Because of their lack for an enzyme called uricase, they are **unable to hydrolyze the urate crystals** and are stuck with them until the cell undergoes apoptosis.
- **Dying PMNs release A LOT of cytokines which exaggerate the inflammatory reaction suddenly → ACUTE GOUT ATTACK** (also called acute gouty arthritis).
  Note: Now the inflammation is acute and severely painful even at rest.
  The defining feature of an acute gout attack is the encapsulation of urate crystals by PMNs and the release of inflammatory cytokines.
- If the patient's hyperuricemia is left untreated, **the crystals can aggregate and form larger bodies called *tophi*** (singular: *tophus*). Tophi give joints the pathologic appearance of gout, where the joint swells to look like a sphere.

Treatment:

There are two families of drugs used to treat gout, but **they are not to be used in combination, each has its own function and conditions for use!**

1. **Urate lowering drugs**: from their name, you can conclude that they lower the serum level of uric acid and therefore the crystals can dissolve again into the blood, **reducing their size** until they vanish. Are used to **manage hyperuricemia**.
2. **Acute arthritis drugs**: manage acute inflammatory attack of gout.

BEWARE: Since we said that the two drug groups aren't to be used together, and we use the acute arthritis drugs for acute gout attacks (makes sense it's in the name), you might notice that these drugs don't actually work to manage hyperuricemia. Why don't we try to reduce the crystals' sizes from the get-go? That is because if the crystals get smaller, they become freer to move around the joint and redistribute, which exposes them more to phagocytosis and this induces more inflammation, meaning more pain that the patient can't withstand. Therefore, it is CRUCIAL to control the inflammation for about 2 weeks before starting to address the crystals, to make sure the patient doesn't suffer another painful attack.

Now we understand that urate lowering drugs:

- Prevent arthritis, tophi & stone formation by lowering total body pool of uric acid, but,
- Are **not indicated after first attack**, because
- Initiation of therapy can worsen or bring on acute gouty arthritis
- And thus, **have no role to play in managing acute gout**.

Therefore, the first-line treatment for a gout patient is using acute arthritis drugs, and these include as you might expect **steroids** and **NSAIDs**, as well as a very old drug called ***colchicine***.

Colchicine: is a plant alkaloid that has been used as a drug for a vey long time, although its use has dropped lately because of numerous adverse effects. It is used to manage inflammation in acute gout and not to reduce uric acid levels. **It is an anti-inflammatory drug!**

- Mechanism of action:
    - **Prevents microtubule depolymerization** by binding to tubulin, this has two applications:
    - Prevents anaphase because microtubules can no longer breakdown and pull chromosomes apart. [Anaphase: a stage in cell replication where sister chromatids move to opposite poles of the cell]
    - Prevents cytokinesis (cell movement) because cytoskeleton can no longer rearrange itself.
    - This mechanism is also used by other plant alkaloids like *Taxol* which is an anti-cancerous drug, but ***colchicine*** **is very selective to PMNs** and is therefore not effective as an anti-cancerous agent but works great in gout to reduce inflammation.

- Result:
    - **Reduces inflammatory response to deposited crystals.**
    - Diminishes PMN phagocytosis of crystals.
    - Blocks cellular response to deposited crystals.
    - PMNs can no increase in number.
- Adverse effects (similar to anticancer drugs):
    - Moderate doses cause **GI upset** (due to its antimitotic activity, it halts epithelium renewal), diarrhea, nausea, and neutropenia.
    - High doses can **damage bone marrow** leading to ablastic anemia and cause alopecia (hair loss).

      Also, when *colchicine* is in given in high doses, it would be concentrated enough in the blood to be filtered out of the hepatic portal circulation into bile fluids by the liver. Bile containing *colchicine* is secreted into the GI, exacerbating the diarrhea and nausea the patient feels, meaning they become more severe.
    - May include **neuromuscular toxicity** and rhabdomyolysis (death of muscle fibers and release of their contents into the bloodstream)

  Most of these side effects result from inhibition of mitosis.
- Mostly used when steroids (patient has hypertension) or NSAIDs are contraindicated (patient has peptic ulcers or history of MIs).
- More **useful for daily prophylaxis** to prevent recurrent attacks so is administered in a low dose (two 0.6 mg pills one hour apart every 12 hrs).

Good Luck ☺ Don't hesitate to ask me if u have any questions ☺