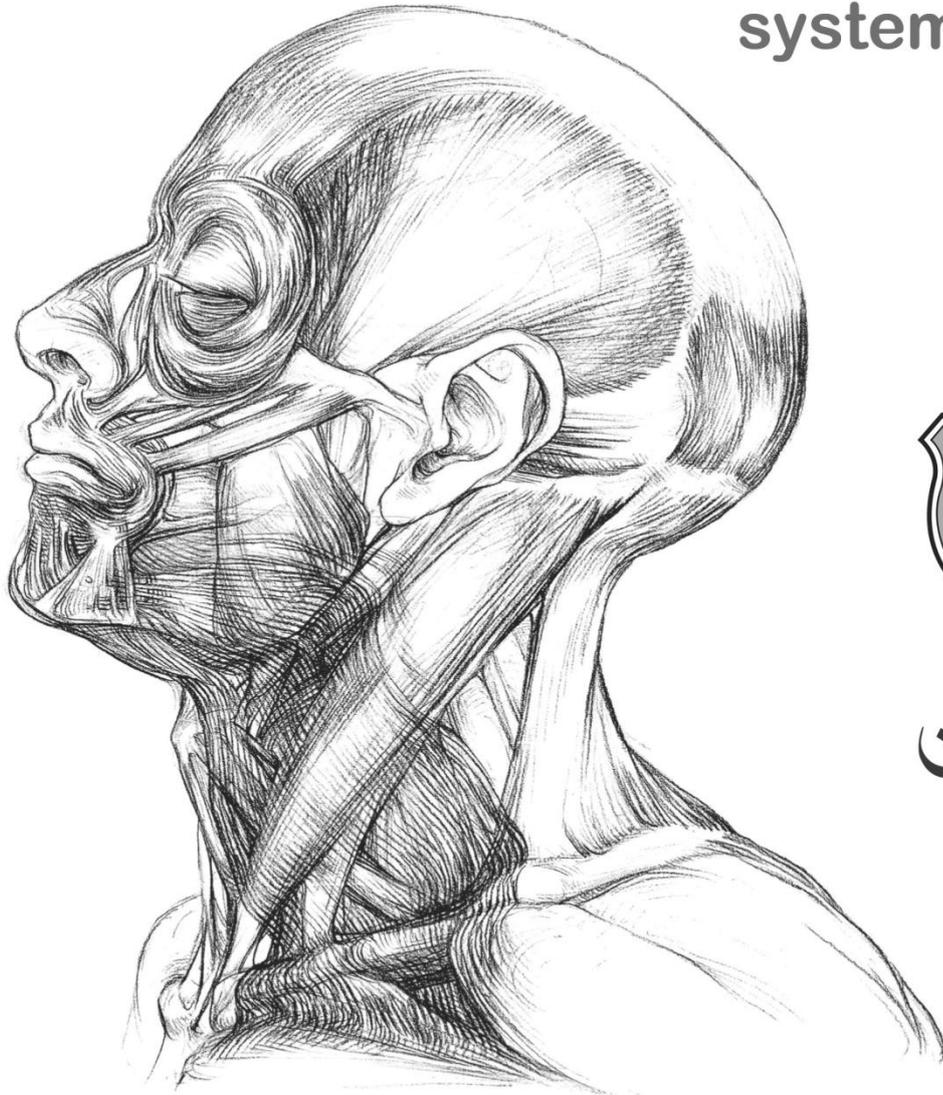


The skin &

Musculoskeletal

system



PHARMACOLOGY

SLIDES
SHEET
LECTURE #5

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Gout

The hallmark of this disease is that we have deposition of monosodium urate crystals in the joints which elicits an inflammatory condition characterized by prostaglandin production, activation of neutrophils and macrophages.

As a result we have a condition of arthritis or synovitis depending on the tissue where deposition of the urate crystals is occurring

These urate crystals come from Uric acid this is why most cases of gout are associated with hyperuricemia (elevated levels of uric acid in the bloodstream)

Note that hyperuricemia isn't always necessarily associated with gout as we have other conditions like asymptomatic hyperuricemia where the patient has elevated levels of uric acid in the blood/urine with no evident clinical manifestations.

The Deposition of urate crystals can happen in places other than joints like soft tissues/under the skin (called tophus), kidneys causing kidneys stones, in cartilage of the ear pinna . These three are the cardinal or the most important manifestations of hyperuricemia.

Today we're going to focus on gout, which is the inflammatory condition that mainly affects the joints:

Which types of joints does gout affects? MAINLY small joints (e.g: the metatarsophalangeal articulations which are the joints between the metatarsal bones of the foot and the proximal bones) but can also happen in big joints (e.g: ankles, elbows) . It should also be mentioned that uric acid deposition can occur in the bursas of such joints (sacs between the tendons and the skin) leading to an inflammation known as Bursitis (e.g: acute olecranon bursitis)

The pathophysiology/ characteristics of gout:

-Affects middle aged people (men are usually more affected than women) associated with inflammation.

-It is characterized by severe pain and intense inflammation of the distal joints that occurs at recurrent episodes called Acute gouty attacks (arthritis) or gouty flares followed by periods of no inflammation.

Gout is one the diseases that's highly influenced by diet as people who consume large amounts of red meat (rich in proteins and purines) are at more chance of developing the disease ESPECIALLY if they have a genetic predisposition . So one of the approaches used in minimizing such attacks is controlling diet (specifically protein consumption).

The process of the inflammatory condition of gout:

For example we have synovitis of the cartilage that includes the cells which produce the synovial fluid (synoviocytes) elicited when such cells encounter the urate crystals and engulf them or when they are stimulated by an inflammatory signal this induces the cells to release prostaglandins, cytokines and certain enzymes such as lysozymes which cause destruction. All this will recruit other inflammatory cells like neutrophils(polymorph neutrophils) which in turn engulf the crystals producing more prostaglandins and leukotrienes further recruiting other mononuclear phagocytes to the site inflammation which will result in propagation of the signal in addition to activation of the osteoclastic activity of the bone and the chondrocytes (by inflammatory cytokines) which will result in bony erosions or resorption of parts of the bones. Finally, the most important characteristic of gout is hyperuricemia as we mentioned above.

(0:00-10:00)

Treatment Of Gout.

Since hyperuricemia is the major problem, lowering the levels of uric acid in the plasma by decreasing its production or increasing its excretion in urine are common approaches to treat gout.

We're going to discuss drugs that either decrease the amount of uric acid produced naturally by the body or enhance its excretion.

The characteristic X-ray appearance of gout shows bony resorptions as radiolucent cysts.

*Note : Take a look at the pictures in the slide .

Pharmacology of gout:

The cardinal signs of hyperuricemia include arthritis, tophi, Nephrolithiasis (the scientific name of kidney stones) which can often lead to nephropathy.

We mentioned that uric acid is the end product in purine metabolism **the pathway of purine metabolism.**

The pathway of purine metabolism:

The purine bases get converted to hypoxanthine which by the enzyme xanthine oxidase gets converted to xanthine and by the end gets converted to uric acid, so pharmacologically xanthine oxidase is a very important target regarding treatment .

Uric acid excretion:

Normally, in the kidneys there are different uric acid transporters, some sites of the glomeruli are specialized in excretion by filtration therefore decreasing the amount of uric acid in the body but we have other areas of tubular reabsorption again followed by tubular excretion in the distal tubules then also in other ducts we have reabsorption.

The physiological net effect of this absorption/reabsorption stages is actually excretion of uric acid, so any imbalance in the above processes may cause more retention of uric acid .

Many drugs are used to affect such process in treatment by targeting reabsorption making them into excretory process or blocking them.(this is one of the mechanism of action of some drugs)

Common drugs used in treating gout

-Colchicine.

-NSAID's

-Steroids.

-Analgesics.

Now, for treating an ACUTE gouty attack (not a complication of hyperuricemia or chronic gout)

So the first thing we do is give the patient something to relieve the pain that is NSAID's, specifically Indomethacin which we mentioned last lectures has a characteristic of increasing the excretion of uric acid thus it can be used to treat such condition. In addition iBuprofen, hydroxysodium, soloredacall and the drug indomethacin help in decreasing inflammation and pain associated with gout each drug is used at a different dose to achieve the required effect.

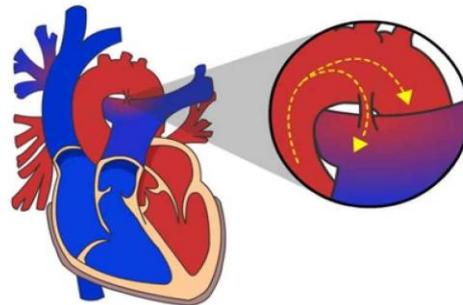
Another drug we previously mentioned separated from NSAID's is Aspirin, at doses the blocks the pain (300ug-1000ug or 200 ug) aspirin has the ability to cause the deposition of uric acid in the kidneys causing kidney stones , this is why aspirin is contraindicated in treating inflammatory conditions of gout while at higher doses (above 3.9 or 4) it has excretory effects but we don't reach such levels due to the harmful effects of aspirin on the GI tract. so as a conclusion aspirin is never used in treating acute gouty arthritis even in reducing the pain.

There's one point we want to recall regarding indomethacin and pregnancy, we mentioned that it's categorized grade C teratogenic in the first and second trimester, and grade D in the last trimester mainly because it causes early closure of *ductus arteriosus* (a blood vessel in the embryo that connects the pulmonary artery to the

descending aorta) because what makes this ductus open are the vasodilatory prostaglandins secreted from the placenta.

In other conditions where the fetus is born with a “patent” (open) ductus arteriosus, Indomethacin in this case can be used as a therapy to assist in its closure (some studies say ibuprofen can also be used), if drugs don't work in closing the vessel we have to revert to another solution or intervention like surgery.

Patent Ductus Arteriosus



*Note : So as we can see in pharmacology any drug can be toxic at a certain dose/condition but also therapeutic at different dose/condition.

(10:00-21:00)

back to gout...

Other than NSAID's, a drug called colchicines (natural product) that acts by preventing the polymerization of microtubules by binding to tubulin (critical for the mitotic spindle formation and mitosis) is used in treating gout but here we're not concerned with the mitotic spindle formation instead with the polymerization of microtubels in pseudopods and important for the process of phagocytosis in macrophages, by inhibiting this process, the macrophages won't be able to engulf the deposited urate crystals.

-Colchicine is actually a naturally occurring product that comes from a plant meroxacolchicin

It is similar to vincristine (a chemotherapeutic agent) which is also an inhibitor of spindle formation but with different chemical structure and source.

Adverse effects of colchicines:

-bone marrow suppression, aplastic anemia, thrombocytopenia, diarrhea, nausea, vomiting due to anti-proliferative effects on the cells of the GI tract rather than ulcers like NSAID's, rarely affects the hair because the doses we're using here are so much lower than the ones used in chemotherapy but we often keep in mind the bone marrow suppression issue monitoring the WBC's, RBC's and platelet counts.

-it can also cause muscular weakness even though the predominant filaments are actin and myosin in muscle tissue, we do have tubulin in the cytoskeletal structure.

Although we use it in gouty arthritis for treating inflammation, it's not an analgesic and it doesn't work for hyperuricemia as it doesn't affect uric acid levels.

A student's question : "why don't we use opioids like morphine for relieving the pain of labor?"

Opioids are not associated with teratogenicity it also has a high risk on the baby in terms of developing addiction not teratogenicity.

One of the things we're concerned about is the patient's whole immunity since colchicine inhibits the proliferation of WBC's.

(21:00-30:00)

When do we use colchicine?

-Acute gouty arthritis at high doses not only during the attack but also between the attacks as prophylaxis (at lower doses 0.6mg) to prevent the recurrence. But a very important note is that colchicine must be used at early onset of the attack as it might have no effect if used after more than 12-24 hours after the attack, since the inflammatory condition has propagated and cells have divided and started to phagocytose, We also can use steroids to inhibit inflammation in the patient.

We mentioned that one of the ways to reduce hyperuricemia is decreasing uric acid production, one of the drugs that act in such mechanism is Allopurinol, an inhibitor of the enzyme *xanthine oxidase* used mainly in the prevention of attacks not for acute attacks,

why?it can cause exaggeration of the gouty attack. So in conclusion, allopurinol isn't used in attacks but after giving the patient steroids and NSAID's it is then given as a prophylactic agent.

-taken orally since IV administration was associated with cytotoxicity and considered pregnancy category C.

When do we use allopurinol?

Mainly in treating hyperuricemia of gout but if we have other conditions, we can use it to manage hyperuricemia associated with the use of some chemotherapeutic agents, and also used to prevent calcium oxalate kidney stones.

Allopurinol's adverse effects: (in general less severe than colchicine's) includes the common side effects (nausea,vomiting,...) but some people rarely develop a serious rash called *toxic epidermonecrosis* (commonly termed Steven Johnson's syndrome) where the epidermis of the skin detaches so it's very important if the patient develops a rash that you stop the drug immediately!

Other rare side effects include hepatotoxicity, bone marrow suppression(but to a less extent than colchicine), Vasculitis (inflammation of blood vessels), and sometime drug interactions with certain antibiotics, diuretics "thiazides" that counter act its effect on uric acid by reabsorption of Na⁺ along with uric acid by certain transporters in the kidneys. One other important drug interaction azothioprinemer captopurine a drug used to treat inflammatory conditions like reumatoid arthritis or inflammatory bowler disease such as crohns disease ulcerative colitis celiac disease, this drug gets converted in the body to its active form "mercaporporien", from its name it has purine that is going to be degraded by *xanthine oxidase*, mercaptopurien is actually a toxic drug if increased in concentration so if the patients is taking allopurinol (which inhibits xanthine oxidase) mercaptopurine won't be degraded leading to toxicity.

* Look at the Picture in the slide about Steven Johnsons syndrome: Skin detachment associated with hypersensitivity to allopurinol that first manifests as a skin rash.

(30:00-40:00)

Deoxystat:

Also a xanthine oxidase inhibitor with a different chemical structure that doesn't target the purine pathway so it's has less side effects.

Minimal adverse effects including headaches, diarrhea and nausea.

the main problem we face sometimes when prescribing these drugs is that patients may have flare ups instead of relief, the problem is these drugs highly depend on the compliance of the patient because some patients only take drugs during that attack and after feeling a little better they stop the drug which leads to these flare ups (approximately 80% of patients do not comply).

Pinuricase

Uricase is an enzyme that's found in some bacteria and porcines (a porcine is any tissue taken form pigs) it destructs uric acid generating urea which is easily excreted form the body .

Polyethylene glycol (PEG) is added to uricase to increase its half life since its degraded rapidly in plasma.

When do we use this drug?

Its only available IV and most of the times used to treat “resistant gout” which is gout that's not responding to any treatment, and its recently approved but it's still under clinical trials to asses its adeverse effects.

Moving on to drugs that enhance the excretion of uric acid that are parts of uricuri therapy which is moderately effective with a significant adverse effect which is nephrolethiasis mainly because elevation of uric acid levels in urine may eventually lead to deposition of the crystals in the kidneys increasing the chance of kidney stones so such therapy is contraindicated for compromised kidneys and elderly patients as the Kinsey functioned deteriorates with age.

-trobinsin : a drug that affects tubular reabsorption by incerasing uric acid concentration in urineand decreasing its concentration in serum.

Clinical Case:

A 55 years old man presented to you after having a 12 hours pain in his toes and ankle, he went to bed feeling fine but he feels now that his big toe is broken, he also has a previous medical history of such pain in his hands and wrist, so what did his doctor prescribe him?

The doctor prescribed steroids (or NSAID's, ibrufen) and after 10 days the pain resolved and the doctor changed to low doses of allopurinol and colchicine as prophylaxis.

Good luck