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

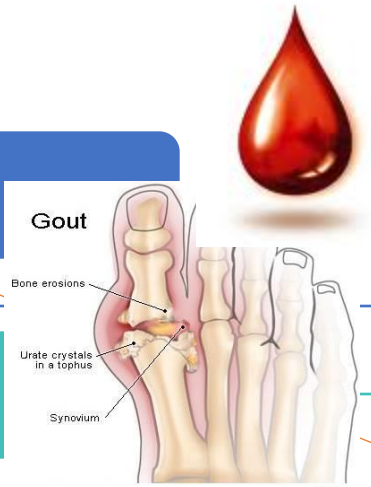
✓ List the drugs that can precipitate gout

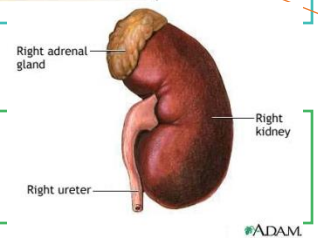
What is gout?

- Inflammatory arthritis
- Due to monosodium urate crystal deposition in tissues (joints & kidney)
- Presents with acute self-limiting attacks of severe pain
- Chronic – causes tophaceous deposits, joint damage and chronic pain

What is gout?

- High blood uric acid level
- Acute arthritis
- monosodium urate stone in kidney
- ♂ > ♀





Breakdown of product of the body's **purine** (nucleic acid) metabolism.

Risk factors (aetiology)

- Male/post menopausal
- Metabolic syndrome
- Diet
  - High purine intake
  - Alcohol (beer/spirits)
- Drugs, including:
  - Diuretics
  - Low dose aspirin
  - Ciclosporin
- Increased cell turnover (malignant tumors)
- Genetic predisposition: Lesch Nyhan syndrome
- Lead (saturnine gout)

Idiopathic decrease in uric acid excretion 90%

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 can lead to deposition of sodium urate crystals in tissues, especially the joints and kidney.

- 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**

Anti-inflammatory drugs

In acute attack

- NSAIDs
- Cortecosteroids
- Colchicine

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.**

Colchicine

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: 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, then after one hour: one tablet, then after 12hs: one tablet /12 hs**

- **Disadvantages:**

- 1- Slow onset 2- Sever side effects

- FAD recommended to stop using colchicine, it is a second choice after corticosteroids and NSAIDs.

Therapeutic uses:

- The anti-inflammatory activity of colchicine is specific for gout, usually alleviate the pain of acute gout within 12 hours.

(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.

Avoided in patients with a creatinine clearance of less than 50 ml/min.

Adverse effects:

- **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
- **Overdose of colchicine:** kidney damage, CNS depression, intestinal bleeding and death: due to muscular paralysis and respiratory failure.
- PRECAUTIONS: The drug should not be used in **pregnancy**, and it 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
- 2- Secondary hyperuricemia: tumor lysis syndrome, Lesch-Nyhan syndrome
- **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.

Adverse effects:

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:**0.5 g/day: proben tab. 500mg**
2-3 tab./day

➢ Sulfinpyrazone: a derivative of phenylbutazone

Adverse effects:

Probenecid and sulfinpyrazone

- Gastric distress
- Probenecid blocks the tubular secretion (excretion) of penicillin and is sometimes used to increase levels of the antibiotic.
- It also inhibits excretion of naproxen, ketoprofen, and indomethacin.
- **Precautions during probencid therapy????**

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

•**Indication**: In chronic gout: sever and complicated cases

Drugs contraindicated in gout

- These drugs may precipitate an acute attack of gout by blocking the renal tubular elimination of urates, thus, raising serum uric acid concentrations.

They include:

- Thiazide and loop diuretics.
- Salicylates in small dose.
- Acetazolamide.
- Pyrazinamide (antituberculous drug)

Thank you

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