DRUGS FOR GOUT

Learning objectives

1. Pathopysiology of gout
2. Drugs that precipitate gout
3. Drugs used for acute gout
4. Colchicine in acute attack of gout
5. Management of chronic gout
6. Probenecid and the uricosuric agents

Gout is a metabolic disease characterized by hyperuricemia & episodes of recurrent acute arthritis due to deposition of urate in joints & cartilage (especially of big toe).
Hyperuricemia & gout depend on two processes:
1. Overproduction of uric acid
2. Underexcretion of uric acid

Pathophysiology

*The inflammatory process is infiltration of leukocytes inside the synovial cavity, these cells phagocytize urate crystals & then breakdown causing release of destructive lysosomal enzymes, PGs & IL-1.
When hyperuricemia is chronic, large & gritty deposits (known as tophi) may form in affected joints; deposition of urate crystals in kidney causes renal damage.

Drugs that precipitate gout

1. Overproduction of urate- due to excessive cell destruction releasing nucleic acids, occurs when myeloproliferative or lymphoproliferative disorders are treated by drugs.
2. Underexcretion of urate- is caused by:
a. Thiazide & loop diuretics
b. Low doses of aspirin
c. Ethambutol & pyrazinamide
d. Nicotinic acid, ciclosporin
e. Alcohol- increases urate synthesis & also causes a rise in blood lactic acid that inhibits tubular secretion of urate
*Food also precipitate gout especially those with excess purines (red meat, sea food, legumes)

***Drugs that have a mild uricosuric effect & increase renal clearance of urate are losartan & fenofibrate.**

Drug management:

1. To relieve acute gouty attacks (anti-inflammatory drugs e.g. indometacin, diclofenac, naproxen, piroxicam) or colchicine or oral corticosteroids
2. To prevent urate synthesis e.g allopurinol, febuxostat
3. To promote urate elimination (uricosuric drugs) e.g. probenecid, sulphinpyrazone

Treatment of acute gout

1. NSAIDs are highly effective, terminating attack in few hours; early treatment is important
Indometacin is first choice orally; naproxen, diclofenac, piroxicam & etoricoxib are effective alternatives.
***Aspirin, is not used, because low doses cause urate retention**

2. Colchicine is an alternative when NSAIDs are contraindicated.
It is anti-inflammatory drug specific for gout, it is an alkaloid from autumn crocus (*Colchicum autumnale*)

Mechanism of action

It is not well understood, but relates to its effects on neutrophils (which play a prominent role in the pathology of gout). It inhibits the assembly of microtubules, thus interfering with mitotic spindle formation and arresting cell division as well as inhibiting cell migration.
*It rapidly relieves pain & inflammation most effectively if used within 24h of onset of acute attack; inflammation disappears completely within 2-3 days. This swift effect confirms diagnosis because non gouty arthritis is unaffected, though failure doesn't prove the patient is free of gout.

Pharmacokinetics

is absorbed from gut, concentrated in kidney, spleen, liver & GIT, some metabolized in liver & some excreted unchanged in bile & reabsorbed from gut, this enhances gut toxicity. Majority is excreted in feces, 15-30%in urine

Side effects

Abdominal pain, nausea, vomiting, the most common is diarrhea (may be bloody) due to inhibition of mitosis in rapidly proliferating cells of intestinal mucosa (this usually responds to reduction of dose)
*iv colchicine causes less GIT toxicity

Management of chronic gout

1. Treatment of risk factors for hyperuricemia which include:
   a. obesity
   b. hypertension
   c. excessive alcohol intake
   d. high dietary intake of purines
2. Drugs

***Attention to these factors will prevent further attacks**

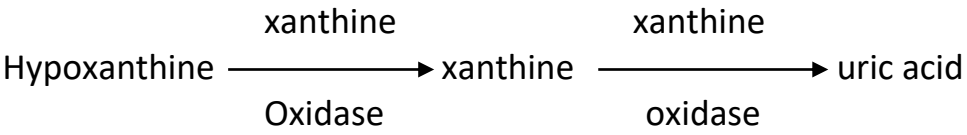
***Rapid lowering of plasma uric acid by any means may precipitate acute gout, probably by causing dissolution of tophi. Thus a NSAID for 6 weeks or colchicine for 6 months must be prescribed concomitantly with uric acid reducing medication.**

Drugs for chronic treatment of gout

1. Prevention of uric acid synthesis

a. Allopurinol (Zyloric)

It inhibits xanthine oxidase (enzyme that converts xanthine & hypoxanthine to uric acid)



Uses

1. recurrent gout
2. prevents hyperuricemia due to diuretics
3. can be combined with uricosuric agent
4. during treatment of myeloproliferative disorders when cell destruction creates a high urate load

Side effects

Precipitation of acute gout, allergic reactions (Allopurinol hypersensitivity syndrome) are uncommon but may be severe (exfoliative rash, arthralgia, fever, lymphadenopathy, vasculitis & hepatitis); deaths have been reported

b. Febuxostat (Adenuric, Uloric)

Is a selective xantine oxidase inhibitor, licensed in Europe in 2008 & in USA in 2009, is recommended for patients who are intolerant to allopurinol.

2. Uricosuric drugs

a. Probenecid (benemid)

It inhibits urate reabsorption & increases its excretion in urine

Pharmacokinetics is rapidly absorbed after oral administration, is highly protein bound.

***High fluid intake should be taken to prevent dangers of mechanical obstruction or stone formation**

Side effects GIT upset, allergy, drowsiness, renal injury from deposition of urate in kidneys

Contraindications 1. severe renal impairment
2. patients with renal calculi

Drug interactions

It prolongs effect of organic acids e.g. penicillins, indometacin, cephalosporins, so the dose of these drugs should be adjusted.

b. Sulfinpyrazone (a metabolite of phenylbutazone)

Acts like probenecid, it lacks analgesic & anti-inflammatory actions, so is useless in acute gout.

It is a potent uricosuric, alkalinization of urine & high fluid intake is necessary to prevent crystalluria

Side effects gastric upset, risk of uric acid deposition in kidney

*It is contraindicated in active peptic ulcer

***Prolonged use of allopurinol & uricosuric agents can decrease size of tophi & even removed.**

Short essay questions

1.Write on the mechanism of action & adverse effects of colchicines
2.List the drugs that precipitate gout

MCQ

1.Uricosuric drugs include
- **T** a.Sulfinpyrazone
- **T** b.Aspirin in high doses
- **F** c.Allopurinol
- **T** d.Fenofibrate
- **F** e.Naproxen

2.Drugs used in acute gout
- **T** a.Indometacin
- **F** b.Sulfasalazine
- **F** c.Allopurinol
- **T** d.Colchicine
- **F** e.Aspirin