



# **Drugs Used to Treat Gout**

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- Gout is a metabolic disease characterized by recurrent episodes of acute arthritis due to deposits of monosodium urate in joints and cartilage.
- Uric acid renal calculi, tophi and interstitial nephritis may also occur.
- Gout is usually associated with a high serum uric acid level (hyperuricemia), a poorly soluble substance that is the major end product of purine metabolism

**Hyperuricemia occur through two mechanisms:**

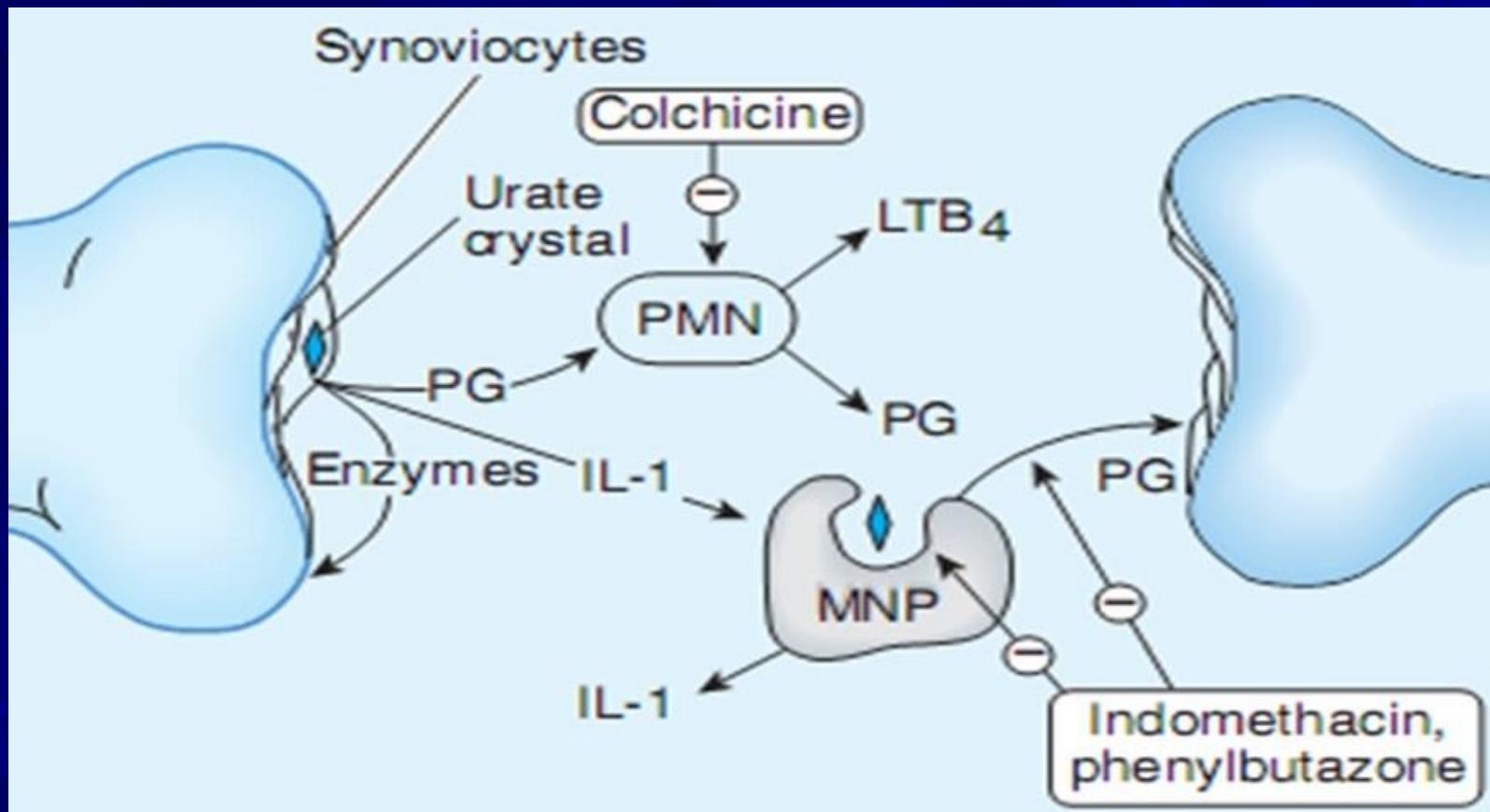
1. Excessive uric acid production
2. Impaired renal excretion of uric acid

## Acute Attacks

- Are precipitated by crystallization of sodium urate (the sodium salt of uric acid) in the synovial space .
- Deposition of urate crystals promotes inflammatory processes.
- Feature of inflammatory processes is infiltration of leukocytes inside of synovial cavity , these cells phagocytize urate crystals and then break down, causing release of destructive lysosomal enzymes

- Synoviocytes damaged by uric acid crystals release prostaglandins (PG), interleukins (ILs), and other mediators of inflammation.
- Polymorphonuclear leukocytes (PMN), macrophages and other inflammatory cells enter the joint and also release inflammatory substances, including leukotrienes (eg, LTB4), that attract additional inflammatory cells.
- Colchicine acts on microtubules in the inflammatory cells.
- NSAIDs act on cyclooxygenase-2 (COX II) and inhibit PG formation in all of the cells of the joint.

## Pathophysiologic Events in Gouty Joint



## **Gout Progresses Through Four Stages:**

1. Asymptomatic hyperuricemia.
2. Attacks of gouty arthritis.
3. Asymptomatic intercritical period, in which symptoms subside.
4. Tophaceous gout, is characterized by development of tophi in joints.

## **Aims of the Treatment of Gout:**

1. Relieve acute gouty attacks
2. Prevent recurrent gouty episodes and urate lithiasis.

## Treating Acute Gout

- Indomethacin is largely replace Colchicine in the treatment of acute gouty attacks. it decrease movement of granulocytes into the affected area
- Colchicine was the primary treatment for many years,it relief acute gouty attacks, within hours, inflammation disappears completely within 2-3 days.
- Intra-articular administration of glucocorticoids (when only one or two joints are affected) is also appropriate in the acute Gout

## Colchicine

- Colchicine relieves the pain and inflammation of gouty arthritis in 12-24 hours without altering the metabolism or excretion of urates and without other analgesic effects.
- Used for the treatment of acute gouty attacks as well as chronic gout.
- Have prophylactic effect that reduces the frequency of acute attacks and relieves pain.

## Pharmacokinetics

- Rapidly absorbed after oral administration
- Half-life of 9 hours.
- Metabolites are excreted in the intestinal tract and urine.

## Pharmacodynamics

- Colchicine produces its anti-inflammatory effects by binding to the intracellular protein tubulin, thereby preventing its polymerization into microtubules (the structure required for cellular motility and cell division) and leading to the inhibition of leukocyte migration and phagocytosis.
- In the absence of leucocytes, there is no phagocytosis of uric acid and no subsequent release of destructive lysosomal enzymes. Leucocytes migration is inhibited by disruption of microtubules.
- Inhibits the formation of leukotriene

## Indications

Although colchicine is more specific in gout than the NSAIDs, NSAIDs (eg, indomethacin and other NSAIDs [except aspirin]) are sometimes used in its stead because colchicine is associated with diarrhea

- Colchicine is now used between attacks (the “intercritical period”) for prolonged prophylaxis (at low doses).
- It is effective in preventing attacks of acute Mediterranean fever
- Sarcoid arthritis
- Hepatic cirrhosis.

## Uses and Dosage of colchicine

- **Prophylaxis:** 0.6 mg one to three times daily.
- **Terminating a gouty attack:** 0.6 or 1.2 mg, followed by 0.6 mg every 2 hours until pain resolves, or nausea and diarrhea appear.

**Note:** In February 2008, the FDA requested that intravenous preparations containing colchicine be discontinued in the USA because of their potential life-threatening adverse effects. Therefore, intravenous use of colchicine is not recommended. In July 2009, the FDA approved colchicine for the treatment of acute gout, allowing Colcrys (a branded colchicine) marketing exclusivity in the USA.

## Adverse Effects of Colchicine

- Nausea, vomiting, diarrhea and abdominal pain, result from injury to the rapidly proliferating cells of the GI epithelium.
- Hepatic necrosis
- Acute renal failure
- Disseminated intravascular coagulation
- Seizures
- Colchicine may rarely cause hair loss (alopecia)
- Bone marrow depression
- Myopathy
- Fetal harm (avoided during pregnancy)
- Extravasation can cause local necrosis (intravenous administration of colchicine)
- Acute overdose is characterized by burning throat pain, bloody diarrhea, shock, hematuria, oliguria and Fatal ascending central nervous system depression

**Note:** Since microtubule required for cell division, colchicines is very toxic for any tissue that has a large percentage of proliferating cells. Disruption of cell division underlies the GIT toxicity of colchicine.

## NSAIDs in Gout

- Inhibit prostaglandin synthase, indomethacin and other NSAIDs also inhibit urate crystal phagocytosis.
- Aspirin is not used because it causes renal retention of uric acid at low doses (less than 2.6 g daily)
- All NSAIDs except aspirin, salicylates and tolmetin use to treat acute gouty episodes.
- Indomethacin is used in the initial treatment of gout as a replacement for colchicine. For acute gout, 50 mg is given three times daily; when a response occurs, the dosage is reduced to 25 mg three times daily for 5-7 days.
- Oxaprozin should not be given to patients with uric acid stones because it increases uric acid excretion in the urine.

## Uricosuric Agents (Probenecid, Sulfinpyrazone)

- Drugs that increase the excretion of uric acid.
- They decrease the body urate in patients with tophaceous gout or in those with frequent gouty attacks.

## Pharmacokinetics

- Probenecid is completely reabsorbed by the renal tubules and is metabolized slowly with a terminal serum half-life of 5-8 hours.
- Probenecid decrease secretion of weak acids & cause prolong penicillin blood levels.
- Sulfinpyrazone or its active hydroxylated derivative is rapidly excreted by the kidneys.

## Pharmacodynamics

- As the urinary excretion of uric acid increases, the size of the urate pool decreases
- Probenecid prevents formation of new tophi and facilitate regression of tophi that have already formed.
- Increase in uric acid excretion, decrease the deposits of urate pool, relief of arthritis and the remineralization of bone occurs .

- The drug may exacerbate acute episodes of gout, therefore treatment should be delayed until the attack has been controlled.
- The formation of renal stones is augmented, the urine volume should be maintained at a high level and at least early in treatment, the urine pH should be kept above 6.0 by the administration of alkali.

## Indications

- Uricosuric therapy should be initiated in gouty patients with under excretion of uric acid when allopurinol or febuxostat is contraindicated or when tophi are present.
- NOTE: Therapy should not be started until 2-3 weeks after an acute attack

## **Adverse Effects of Uricosuric Agents (Probenecid, Sulfinpyrazone)**

1. GI irritation (sulfinpyrazone is more than probenecid)
2. Hypersensitivity reactions (rash)
3. Nephrotic syndrome has occurred after the use of probenecid (due to deposition of urate in the kidney) this risk can be minimized by consuming 2.5-3 lit. of fluid daily during the first days of treatment
4. Aplastic anemia (rarely)

## Dosage

- Probenecid is usually started at a dosage of 0.5g orally daily in divided doses, progressing to 1g daily after 1 week.
- Sulfinpyrazone is started at a dosage of 200 mg orally daily, progressing to 400-800 mg daily. It should be given in divided doses with food to reduce adverse GI effects.

## Cautions

It is essential to maintain a large urine volume to minimize the possibility of stone formation.

# **Xanthine Oxidase Inhibiter Allopurinol**

The preferred therapy for gout during the period between acute episodes is allopurinol, which reduces total uric acid body burden by inhibiting xanthine oxidase.

## **Xanthine Oxidase Inhibiter**

### **Allopurinol**

#### **Pharmacokinetics**

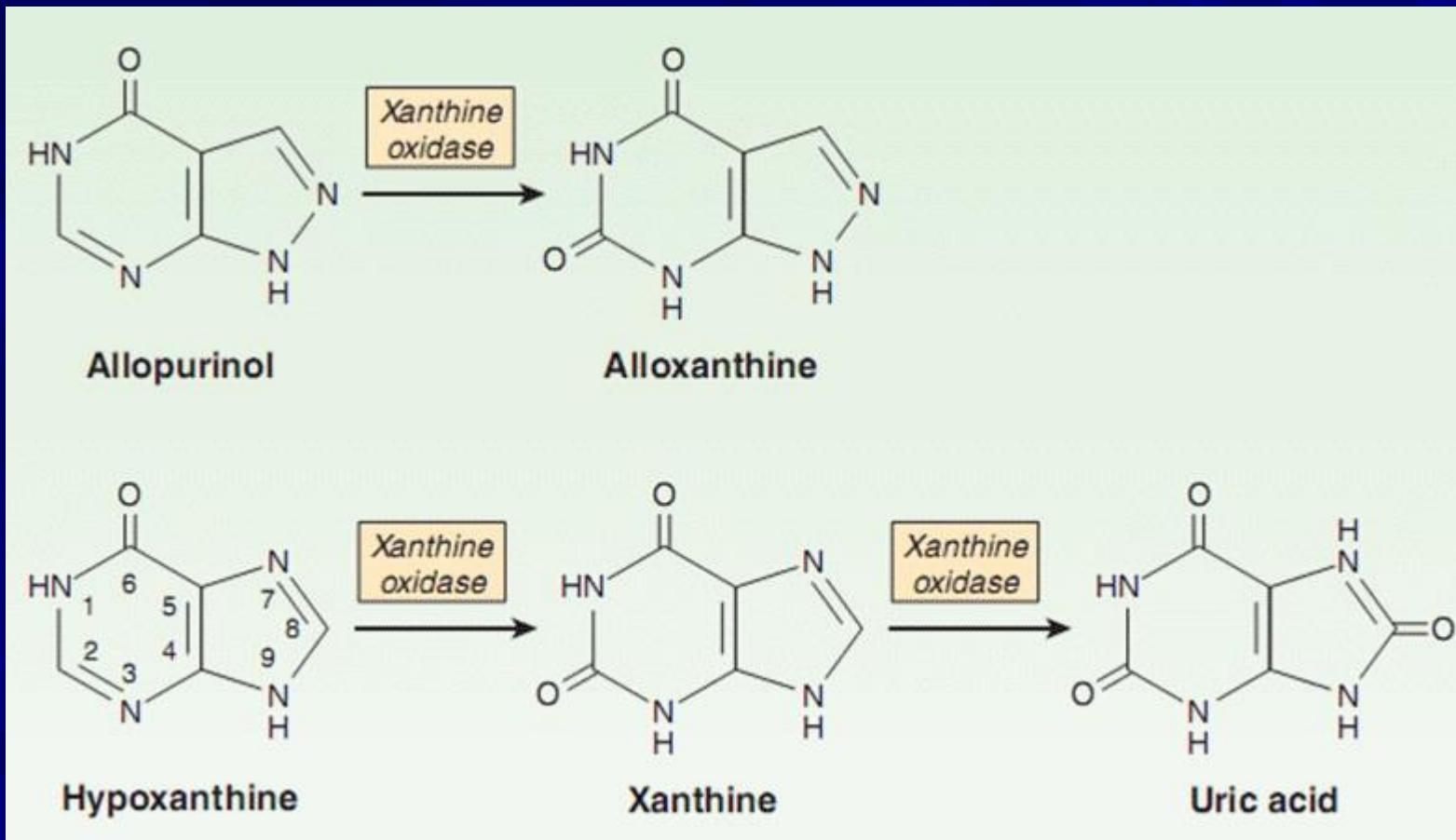
- Allopurinol is approximately 80% absorbed after oral administration
- Half-life of 1-2 hours.
- Allopurinol is metabolized by xanthine oxidase, but the resulting compound, alloxanthine, retains the capacity to inhibit xanthine oxidase and has a long enough duration of action so that allopurinol is given only once a day.

## Pharmacodynamics

➤ Allopurinol and its active metabolite-alloxanthine- reduce uric acid production, by inhibition of xanthine oxidase, an enzyme required for uric acid formation.

NOTE: Xanthine oxidase catalyzes the final two reactions that lead to formation of uric acid from breakdown of DNA

# Inhibition of Uric acid Synthesis by Allopurinol



# Indications

- Allopurinol is often the first-line agent for the treatment of chronic gout in the period between attacks and it aims to prolong the intercritical period.
  - Allopurinol is effective in the treatment of primary hyperuricemia of gout and hyperuricemia secondary to other conditions(that associated with certain malignancies (those in which large amounts of purines are produced, particularly after treatment with chemotherapeutic agents) or in renal disease.
  - This agent is the drug of choice in those with a history of kidney stones or if the creatinine clearance is less than 50 mL/day.
  - When initiating allopurinol, colchicine or NSAID should be used until steady-state serum uric acid is normalized or decreased to less than 6 mg/dL and they should be continued for 3-6 months or even longer if required

- Allopurinol is also used as an antiprotozoal agent
- prevent the massive uricosuria following therapy of blood dyscrasias that could lead to renal calculi.

## Dosage

- The initial dosage of allopurinol is 100 mg/d. It should be titrated upward until serum uric acid is below 6 mg/dL; this level is commonly achieved at 300 mg/d, doses as high as 800 mg/d may be needed.
- Colchicine or an NSAID should be given during the first several weeks of allopurinol therapy to prevent the gouty arthritis episodes that sometimes occur.

## Adverse Effects

1. GI intolerance including nausea, vomiting and diarrhea
2. Peripheral neuritis
3. Necrotizing vasculitis
4. Bone marrow suppression
5. Aplastic anemia (rarely)
6. Hepatic toxicity
7. Interstitial nephritis.
8. An allergic skin reaction ,pruritic maculopapular lesions occurs in 3% of patients
9. Cataracts (Allopurinol )bound to the lens

## Interactions & Cautions

- When chemotherapeutic purines (eg, azathioprine) are given concomitantly with allopurinol, their dosage must be reduced by about 75%.
- Allopurinol may also increase the effect of cyclophosphamide.
- Allopurinol inhibits the metabolism of probenecid and oral anticoagulants and may increase hepatic iron concentration.
- Safety in children and during pregnancy has not been established.

## **Febuxostat**

**Approved by the FDA in y 2009.**

- Febuxostat is a non-purine xanthine oxidase inhibitor

## **Pharmacodynamics**

- Potent and selective inhibitor of xanthine oxidase, thereby reducing the formation of xanthine and uric acid without affecting other enzymes in the purine or pyrimidine metabolic pathway.

## Pharmacokinetics

- Orally administration.
- Half-life of 4-18 hours, once-daily dosing
- Metabolized in the liver, less than 5% appears as unchanged drug.
- All of the drug and its inactive metabolites appear in the urine

## Indications

- Febuxostat is approved at doses of 40, 80, or 120 mg the treatment of chronic hyperuricemia in gout patients

## Adverse Effects

- Gout flares  
NOTE: prophylactic treatment with colchicine or NSAIDs should be started at the beginning of therapy to avoid this side effect.
- Diarrhea and nausea
- Headache
- Liver function abnormalities

## Pegloticase

- Pegloticase is the newest urate-lowering therapy
- It was approved by the FDA in September 2010 for the treatment of refractory chronic gout

## Pharmacokinetics

- Pegloticase is a rapidly acting intravenous drug, achieving a peak decline in uric acid level within 24-72 hours.
- Intravenous infusion every 2-4 weeks, and can only be used over a limited period of time (e.g. 3-6 months) due to development of anti-pegloticase antibodies that cause infusion reactions.
- Maintain low urate levels for up to 3 weeks

## **Mechanism of Action:**

Ricombinant uricase enzyme that converts uric acid into a more soluble compound that is easier to excrete

## **Indications:**

- Severe treatment-resistant forms of gout (don't respond to multiple other forms of therapy including NSAIDs, allopurinol, colchicine & steroids)
- For rapid de-bulking of tophi in patients with treatment-refractory gout or chronic tophaceous gout

## **Side Effects:**

### **Anaphylaxis & Infusion Reactions**

- Anaphylaxis can occur with any infusion, and typically occurs within 2 hours of the infusion.
- Delayed type hypersensitivity reactions have also been reported.
- Pre medication with antihistamines and corticosteroids to decrease this side effect.