EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 12
219-222
Year: 2019

GOUT-AN UPDATE

Veeramreddy Spandana, Budharam Sindhuja, A. Rajani* and G. Ravi[1]

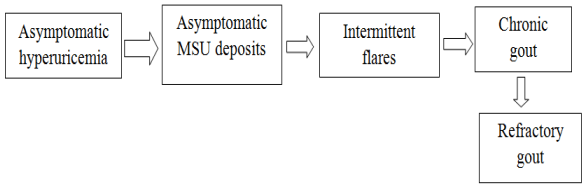
M.Pharm. Ph.D, Associate Professor, Department of Pharmacy Practice, MNR College of Pharmacy, Sangareddy, TS.
[1]Department of Pharmaceutics, MNR College of Pharmacy, Sangareddy, TS.

***Corresponding Author: Dr.A.Rajani** M.Pharm., Ph.D
Associate Professor, Department of Pharmacy Practice, MNR College of Pharmacy, Sangareddy, TS.

Article Received on 09/09/2019 **Article Revised on 30/09/2019** **Article Accepted on 20/10/2019**

Gout can be defined as an arthritic condition resulting from the deposition of monosodium urate (MSU) crystals in the joints, following chronic elevation of uric acid level above the saturation point for MSU.[1]

Phases of Gout



Epidemiology

Gout is the most common inflammatory arthritis affecting men in the developed world and is also the most common crystalline arthropathy.[2] Annual incidence of gout is 2.68 per 1000 persons.

Risk factors[3]

Non modifiable

- Age
- Sex

Modifiable

- Serum urate
- Medications
- Renal and other major organ transplants
- Diet and alcohol intake
- Obesity

Pathophysiology[4]

Uric acid is mainly a by-product from the breakdown of cellular nucleo proteins and purine nucleotides synthesized de novo with about a third coming from the breakdown of dietary purine intake. Uric acid is a weak acid with a pK_a of 5.75, and at the physiological pH of the extracellular compartment 98% of uric acid is in the ionised form of urate. This is mainly present as monosodium urate due to the high concentration of sodium in the extracellular compartment. Human beings and higher primates lack the enzyme uricase that degrades uric acid to highly soluble allantoin resulting in higher concentrations of urate close to the level of solubility. Monosodium urate has a solubility limit of 380µmol/lit, there is a risk of precipitation and formation of monosodium urate crystals.

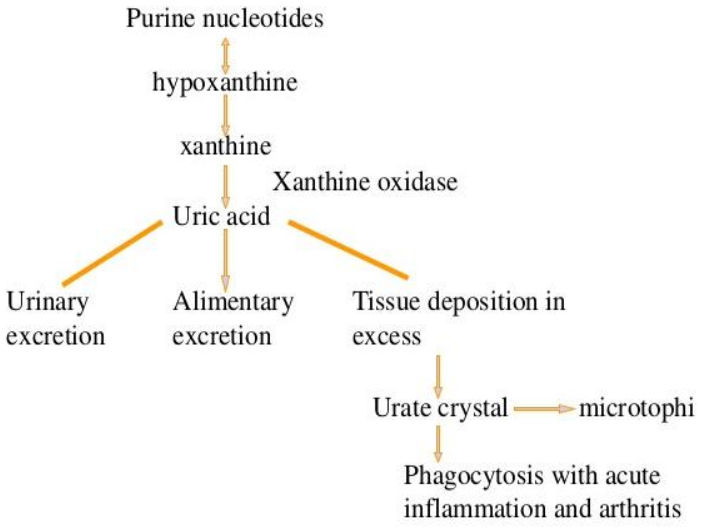
The production of urate is dependent upon the balance between purine ingestion, denovo synthesis in the cells and the actions of xanthine oxidase at the distal end of purine pathway. Xanthine oxidase is the enzyme that catalyses the oxidation of hypoxanthine, the breakdown product from the catabolism of cellular nucleoproteins and purine nucleotides, to xanthine and xanthine to uric acid.

Gout can be classified as primary or secondary, depending on the presence or absence of an identified cause of hyperuricaemia.

Primary gout is not a consequence of an acquired disorder, but is associated with rare inborn errors of metabolism and isolated renal tubular defects in the fractional clearance of uric acid, a rare group of enzyme defects result in an increased de novo purine synthesis such as hypoxanthine-guanine phosphoribosyl pyrophosphate synthetase super activity, glucose-6-phosphatase deficiency and myogenic hyperuricaemia.

Secondary gout is the consequence of the use of drugs or develops as a consequence of other disorders. Certain diseases are associated with enhanced nucleic acid turnover, for example, myeloproliferative and lymphoproliferative disorders, psoriasis and haemolytic anemia and can lead to hyperuricemia. Renal mechanisams are responsible for the majority of the hyperuricaemia in individuals with over production representing less than 10% of patients with gout. Kidney excretes about two-thirds of the uric acid produced daily with the remainder being eliminated via the biliary tract with subsequent conversion to soluble allantoin by colonic bacterial uricase. Approximately 90% of the daily load of urate filtered by the kidney is reabsorbed.

This reabsorption process is mediated by specific anion transporters such as URAT-1 which is located on the apical side of the renal proximal tubular cells and is an important determinant of urate reabsorption. The URAT-1 transport is targeted by a number of drugs including benzbromarone, probenecid, losartan and sulphinpyrazone.



Pathophysiology of Gout

Clinical manifestations[5]

- Severe pain in your joints.
- Joint stiffness.
- Difficulty moving affected joints.
- Redness and swelling.
- Misshapen joints.
- Low grade fever.

Diagnosis[6]

According to American college of Rheumatology, two clinical algorithms, the Diagnostic Rule and Clinical Gout Diagnosis, were evaluated as tools for diagnosing gout. Both of these algorithms were developed and validated with patients first identified in primary care and whose diagnosis did not include an MSU assessment.

Diagnostic Rule

The diagnostic components of this algorithm include clinical characteristics

- >1 Attack of acute arthritis, maximum inflammation developed within 1 day,
- Redness observed over joints,
- Painful or swollen first metatarsophalangeal joint
- Risk factors (hyperuricemia, male sex, hypertension, or >1 cardiovascular disease event).

Clinical Gout Diagnosis

The diagnostic components of this algorithm include clinical characteristics

- >1 Attack of acute arthritis, maximum inflammation developed within 1 day, monoarthritis/oligoarthritis attack,
- Redness observed over joints,
- Painful or swollen first metatarsophalangeal joint,
- Unilateral tarsal joint attack, tophi.
- Risk factors (hyperuricemia)

Treatment

Goals of therapy

- The goal of treatment is to reduce the uric acid level to less than 6 mg/dl.
- The goal of lowering the blood uric acid is to slowly dissolve joint deposits of monosodium urate.
- Lowering the uric acid will not treat an acute attack but will, over time, prevent additional attacks from occurring.

Pharmacological therapy

Management for the acute attack of gout

Non-steroidal anti-inflammatory drug (NSAID), glucocorticoids and colchicine are all evidence based, cost effective treatment for the acute attack of gout. All the above agents are non-selective inhibitors for the neutrophil driven inflammation that occurs in acute gout.[7]

Colchicine

Colchicine has been found to be efficacious when compared to placebo in randomized controlled trial. It has also been very clearly confirmed that high and low dose of colchicine has similar effectiveness, but low dose of colchicine carries a better safety profile as compared to the high dose.[8] Accordingly, high dose of colchicine should be avoided which carries significant gastrointestinal side effects. The usual dose should be 2-4 tablets a day, which has similar efficacy, but with much less risk of side effect. Intravenous colchicine is

associated with potential fatal adverse event and should be avoided. Also, there is a drug interaction between CYP3A4E-glycoprotein inhibitors and colchicine in particular in the presence of hepatic and renal dysfunction which should be taken into consideration on using colchicine. In mild to moderate renal impairment with GFR >30 ml/min colchicine can be used in reduced dose.

Non-steroidal anti-inflammatory drugs

Most of non-steroidal anti-inflammatory drugs have similar efficacy with regard to treating acute attack of gout. Also it has been found that Cox 2 inhibitor has the same efficacy as conventional non-steroidal anti inflammatory drugs, but with better GI profile. However, all NSAIDs are associated with risks of potential adverse effects and drug interactions particularly in elderly patients and those with chronic kidney disease or diabetes and they should be avoided in patients with renal impairment.[9]

Glucocorticoids

There is no placebo controlled trials for systemic glucocorticoids in gout, but when compared to NSAIDs, glucocorticoids are as effective as NSAIDs and has better safety profile. It has also been found that the ACTH 40 IU intramuscular has significantly faster onset of action as compared to NSAIDs with complete relief of the pain in 3 versus 24 hour respectively.[10] Corticosteroid is a good option for patient with renal impairment or for those at high risk from NSAIDs induced GI side effect. Oral corticosteroid could be used in a dose of around 30 mg daily for about five days to treat any acute gouty attacks. This option is also important for those with moderate to severe chronic kidney disease. Intra-articular glucocorticoids injection is another option which can give an excellent and quick pain relief but this should be avoided in patients with suspected septic arthritis.

Biologics

Anti-interleukin-1 drug (canakinumab) in a dose of 150 mg is more effective than a single IM glucocorticoid steroid injection of triamcinolone 40 mg and has a similar safety profile.[11]

Management of chronic gout

Uricostatic agents

Allopurinol

It is the most well-established and cheap urate lowering agent available and it should be our first line option. Allopurinol dose should be titrated from a starting dose of 100 mg daily and increase by 100 mg monthly until the target serum urate level is achieved with up to a maximum of 800 mg daily.[12] Dose should be adjusted as per renal function. In treating patients with gout, we have to keep in mind that allopurinol at a dose of 300 mg daily will only achieve the serum urate target level of <6 mg/dl (360µmol/l) in around 40% of patients with normal renal function. Increasing the allopurinol dose up to 600 mg daily will achieve the target serum urate level in about 80% of patients who have preserved renal function.

Febuxostat

Like allopurinol, this is a selective xanthine oxidise inhibitor which does not have purine like structure. Febuxostat is usually metabolised by liver. Accordingly, unlike allopurinol, renal elimination has a minor role in febuxostat. Its main adverse effect is rash which could occur in 2% of the patients using it, but without any reported severe reaction. Diarrhoea and elevated liver enzyme occur also in a few patients. Febuxostat has been approved at a dose of 80 mg daily in the States and up to 120 mg daily in Europe. In view of its cost as compared to allopurinol, febuxostat is reserved for patients with allopurinol hypersensitivity, intolerance or treatment failure. Febuxostat at a dose of 80-120 mg achieve the target serum urate level of <6 mg/dl (360µmol/l), whereas most of the patients on allopurinol 300 mg usually fail this target.[13]

Uricosuric therapy

Other urate lowering medication which could be used is the uricosuric agents such as sulfinpyrazone, probenecid and benzbromarone. These agents enhance renal uric acid excretion primarily by decreasing the urate reabsorption in the renal tubules. In patients with adequate renal function, uricosuric agent can be effective.[14] Uricosuric therapy can also provide extra benefit in combination with xanthine oxidase inhibitor in patients who fail to achieve the target serum urate level. Uricosuric agents main disadvantage is related to the increase risk of urolithiasis in particularly in acid urine which is unfortunately a feature of metabolic syndrome which could be associated with gout. Sulfinpyrazone should be used in a dose of 100-200mg daily with food with gradual increment every 3 weeks up to 600mg daily. Probenecid is much less used.

Benzbromarone at a dose of 50-200 mg incremental dose is an important uricosuric agent which could be used in patients with chronic kidney disease with the GFR as low as 20ml/min. Accordingly, it is a valid option for patients with significant renal impairment and in those who cannot tolerate other urate lowing agent or when the s uric acid level target cannot be achieved by using other medications.

Benzbromarone is a highly effective with 100% of patients achieving target urate levels as compared to Allopurinol.[15]

Uricolytics

Uricolytic drugs convert uric acid to allantoin through the actions of the enzyme urate reductase.

Rasburicase

It is the recombinant form of the enzyme urate oxidase is derived from a cDNA code from a modified Aspergillus

flavus strain expressed in a modified strain of saccharomyces cerevisiae. It is given intravenously at a dose of 0.2mg/kg in short courses for 5-7 days. It has a half life of approximately 19 hours.

Polyethylene glycol-uricase

It is a pegylated, recombinant form of uricase. Pegylation of molecules reduces the risk of patients developing auto-antibodies and lengthens the half life of the drug. It is effective in reducing tophi.

Non-pharmacological therapy[16]

- Lose weight
- Drink of glass of skimmed milk a day
- Limit alcohol and foods rich in purines.
- Avoid purine-rich foods such as fatty meats and shellfish
- Avoid stress.
- Exercise frequently
- Get enough rest and sleep
- Try certain herbal and dietary supplements

Prognosis[17]

- Joint damage.
- Joint deformity.
- Loss of mobility or range of motion.
- Bone loss.
- Tophi (chalky lumps or deposits that form underneath the skin)
- Kidney stones.
- Chronic kidney disease.

ACKNOWLEDGEMENTS

Authors are very much thankful to Dr. V. Alagarsamy, Professor & Principal, MNR College of Pharmacy for his constant support and encouragement.

REFERENCES

1. Thomas Bardin, Pascal Richette, Definition of hyperuricemia and gouty conditions. *Wolters Kluwer Health*, 2014; 26(2): 186-191.
2. Gandikota Girish, Katrina N. et al., Advanced Imaging in Gout. *AJR*, 2013; 201(9): 515-525.
3. Kenneth G Saag, Hyon Choi, Epidemiology, risk factors and lifestyle modifications for gout. *Arthritis Research & Therapy*, 2006; 8(1): 1-7.
4. Dalbeth N. Haskard. Mechanisms of inflammation in gout .*Rheumatology*, 2005; 44: 1090-1096.
5. Brian F. Mandell. Clinical manifestations of Hyperuricemia and Gout. Cleveland clinic journal of medicine, 2008; 75(7): 5-8.
6. Abdul-Wahab Al-Allaf. Gout: evidence based update with new therapeutic strategies. *Sudan Med J*, 2012; 48(3): 165-175.
7. Liu-Bryan R, Scott P, Sydlaske A, Rose DM et al., Innate immunity conferred by toll-like receptors 2 and 4 and myeloid differentiation factor 88 expression is pivotal to monosodium urate monohydrate crystal-induced inflammation. *Arthritis rheum*, 2005; 52: 2936-46.
8. Terkeltaub RA, Furst DE, Bennett K, et al. High versus low dosing of oral colchicines for early acute gout flare: twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum*, 2010; 62(4): 1060-8.
9. Terkeltaub RA. Clinical practice: gout. *N Engl J Med.*, 2003; 349: 1647-55.
10. Axelrod D, Preston S. Comparison of parenteral adrenocorticotropic hormone with oral indomethacin in the treatment of acute gout. *Arthritis Rheum*, 1988; 31(6): 803-5.
11. So A, De Meulemeester M, Pikhlak A, et al. Canakinumab for the treatment of acute flares in difficult-to-treat gouty arthritis: results of a multicenter, phase II, dose-ranging study. *Arthritis Rheum*, 2010; 62(10): 3064-76.
12. Chao J, Terkeltaub RA. Critical reappraisal of allopurinol dosing, safety and efficacy for hyperuricaemia in gout. *Cur Rheumatol Rep*., 2009; 11: 135-40.
13. Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricaemia and gout. *N Engl J Med*., 2005; 353: 2450-61.
14. Reinders MK, van Roon EN et al., Biochemical effectiveness of allopurinol and allopurinol probenecid in previously benzbromarone treated gout patients. *Clin Rheumatol*, 2007; 26: 1459-65.
15. Perez-Ruiz F, Alonso-Ruiz A, Calabozo M et al. Efficacy of allopurinol and benzbromarone for the control of hyperuricaemia. A pathogenic approach to the treatment of primary chronic gout. *Ann Rheum Dis*., 1998; 57: 545-9.
16. Martin underwood. Diagnosis and management of Gout. *BMJ*, 2006; 332(6): 1315.
17. Gerry R. Boss. Edwin Seegmiller Hyperuricemia and Gout – Classification, complications and Management. *N Engl J Med.*, 1979; 300(6): 1459 - 1468.