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“Gout: Update & Therapeutic Considerations”

January 2014

We periodically review & update consideration of gout for two reasons: 1st it is the most common inflammatory joint disease; 2nd because there are two new drugs that are being used for treatment. Our goals are to revisit this important topic & review treatment options. This lesson provides 1.25 hours (0.125 CEUs) of credit, and is intended for pharmacists in all practice settings.

The objectives of this lesson are such that upon completion the participant will be able to:

1. Define “gout” & describe its characteristics.
2. List symptoms of gout.
3. Discuss drugs used to treat gout.
4. Describe side effects associated with gout drugs.
5. Comment upon MOAs of gout drugs.



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DEFINITION AND INTRODUCTION

Gout is a complex, hereditary disorder of purine metabolism. It is characterized by hyperuricemia (abnormally high amounts of monosodium urate, MSU, in the blood) and the formation of deposits of MSU crystals in the connective tissue and articular cartilage of the joints causing sudden, severe and painful recurring attacks of acute gouty arthritis. The involved joint becomes inflamed, purple-red, tender and swollen. Gout can affect any joint in the body---ankles, hands, wrists, knees elbows and feet. However, about 50% of the cases occur at the base of the big toe.

The word gout was derived from the Latin term "gutta," or the French word "gote" meaning "a drop." The disease was described by Galen and Hippocrates. During the Middle Ages, it was postulated that this condition was due to toxic substances that seeped from the blood into the joint. Today, it is known that this theory is not far from current reality. Some experts speculated that gout was due to food, wine and high living. As a result, it was often referred to as "rich man's disease," or "disease of kings." This label became accepted when some famous individuals like Queen Anne, Michelangelo, Martin Luther, Isaac Newton, Louis XIV, Samuel Johnson, Charles Darwin and Benjamin Franklin were reported to have suffered from gout.

Gout is actually the most common form of inflammatory joint disease. Its incidence has been on the rise in recent decades. It is estimated that approximately 8 million people in the U.S. suffer from gout. It is uncommon in young women. The incidence increases dramatically after menopause at which time the incidence equals that of men over age of 60. Deposition of MSU in the blood continues to increase with age, especially in the presence of conditions common in the elderly such as hypertension, diabetes, cancer and metabolic syndrome. About 2% of men over 30 and 2% of women over 50 years of age have this condition. The incidence increases to 9% in men and 6% in women over the age of 80.

PATHOPHYSIOLOGY

Hyperuricemia occurs as a result of faulty metabolism of purine nucleosides such as adenosine and guanosine.

Adenosine consists of a molecule of adenine attached to a ribose sugar molecule. It is present naturally in all body cells and participates in many physiological processes including energy transfer.

Adenosine Metabolism to Uric Acid

- Adenosine is converted to inosine (via the enzyme adenosine deaminase).
- Inosine is converted to hypoxanthine (via the enzyme purine nucleoside phosphorylase).
- The enzyme (xanthine oxidase) converts hypoxanthine to xanthine.
- Xanthine converts to uric acid.

Guanosine comprises guanine attached to a ribose ring. Like adenosine it is an endogenous purine and is involved in many biochemical processes such as synthesis of protein and nucleic acid. Some antiviral drugs are similar in structure to guanosine. Degradation of guanosine that leads to the formation of uric acid as the end product is similar to that of adenosine.

Guanosine Conversion to Uric Acid

- Guanosine is converted to guanine (via the enzyme purine nucleoside phosphorylase).
- Guanine is converted to xanthine (via the enzyme guanine deaminase).
- Xanthine is converted to uric acid (via the enzyme xanthine oxidase).

The end product in both pathways, uric acid, remains intact in the blood due to the absence of the uricase (urate oxidase), an enzyme that breaks down uric acid in humans. The bodies of most mammals, other than primates, lack uricase. Only a small amount of uric acid in the blood stream is secreted in the intestine where it is degraded by bacterial flora.

The main sources of purine nucleosides are: endogenous sources and dietary sources (exogenous) such as foods like pork, red meat, anchovies, herring, beans, cauliflower, spinach, mushrooms, asparagus and alcoholic beverages, especially beer. About half of the amount of purine in the body is destroyed and replaced each day. Patients, whose bodies overproduce purine as a result of hereditary metabolic factors, lack of certain enzymes, or intake of diet rich in purine, will experience hyperuricemia. It has been reported that strict avoidance of a purine rich diet may reduce serum MSU by at least 1 mg/dl.

About 60% of body urate is eliminated into the urine via the kidney. If the kidneys are not excreting enough uric acid due to renal disease, buildup of uric acid will occur and may lead to crystallization. A uric acid concentration of 6.8 mg/dl is a level at which solubility of uric acid is impaired resulting in precipitation of sharp, needle-like crystals of MSU in the joints, tendons and adjacent tissue.

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The crystals will interact with polymorphonuclear leukocytes resulting in cellular inflammatory processes and release of prostaglandins, lysosomal enzymes and interleukin by polymorphonuclear cells. The crystal deposits within a joint are known as tophi. The tophi can form in the extracellular articular tissue resulting in deformity and damage to hard and soft tissue, especially when they grow in size. Furthermore, the presence of tophi can cause degeneration of cartilage and bone leading to arthritis.

SIGNS AND SYMPTOMS

The initial symptoms of acute gout include an abrupt onset of excruciating pain in a joint. The attack may follow the intake of excessive amounts of alcohol, food rich in purine or following surgery, infection or the intake of diuretics. Some mild pain may precede the attack. After its onset, the pain may intensify and the joint swells, and becomes red purplish in color, tender and warm. Systemic symptoms such as fever, headache, loss of appetite and bradycardia may occur. Once the attack subsides, pruritus, as well as peeling of the skin at the joint may follow. After the initial acute attack, the patient may not encounter additional episodes for periods ranging from months to years. However, if gout becomes chronic, the episodes become more frequent and intense resulting in morbidity, disability and deformity at the joint. The deformity becomes more severe as MSU deposits grow in size.

The presence of hyperuricemia does not mean that gout is inevitable. Occasional gouty attacks may take place in the absence of hyperuricemia. Some hyperuricemic patients may experience only one attack during their lifetime, while others may have repeated attacks. Even though the interval between the initial attack and later ones could be many years, the vast majority of patients experience a subsequent attack within two years. Most first gouty attacks occur in patients who have been hyperuricemic for 20 to 40 consecutive years. The peak age of onset of attacks is 40 to 60 years of age for men and postmenopausal women.

RISK FACTORS THAT MAY RESULT IN HYPERURICEMIA

1. **Increased endogenous production and exogenous intake:** A significant amount of ingested purines in the diet are responsible for 12% of gout cases. Likewise, increased endogenous production of purine by the body has an effect on the levels of uric acid.
2. **Decreased urinary excretion of uric acid:** The overwhelming majority of gout patients experience a defect in urinary excretion of uric acid. This may result from decreased glomerular filtration, decreased tubular secretion, or enhanced tubular reabsorption.
3. **Genetics:** Many people who suffer from hyperuricemia do not develop gout. It has been postulated that genetics plays a role in contributing to the disease. The genes SLC2A9, SLC22A12 and ABCG2 are linked to increased risk for the development of gout.
4. **Gender and Age:** Gout is more common in males than females, and in older patients.
5. **Medications:** Diuretics, regular intake of low doses of aspirin, cyclosporine, niacin and alcohol consumption have been associated with triggering gout attacks.
6. **Medical conditions:** The presence of hypertension, metabolic syndrome, diabetes, hyperlipidemia and arteriosclerosis have been associated with gout.
7. **Obesity:** This is considered a strong risk factor for gout. Some data indicated that gout onset occurred three years earlier in obese patients. Moreover, the onset was 11 years earlier in patients who had been obese since early adulthood. It is also believed that

increased insulin resistance associated with obesity may lead to hyperuricemia and subsequently to gout.

DIAGNOSIS

1. Serum uric acid above 7.5 mg/dl.
2. Increased level of erythrocyte sedimentation rate and white blood cell count during an acute gout attack.
3. Presence of MSU in substances aspirated from the tophi and synovial fluid.
4. X-rays are beneficial in the diagnosis of chronic gout.

TREATMENT

There is no cure for gout, but it can be managed. An acute attack usually resolves spontaneously within a week or two. The majority of patients will have another attack within a year. However, the interval between the first and second attack may be as lengthy as 40 years. The goal of treatment is to alleviate the pain during the attack and to prevent further attacks from occurring.

Pain Relief Medications

The primary drugs for pain relief are NSAIDs & colchicine.

Nonsteroidal anti-inflammatory drugs (NSAIDs): They are used often during an acute attack. These medications act as analgesics, antipyretics and anti-inflammatory agents. In the past, indomethacin and phenylbutazone were widely used for these purposes. Even though both were effective, their safety was questionable. Their serious adverse effects and the introduction of NSAIDs caused their decline.

Indomethacin acts like NSAIDs by inhibiting cyclooxygenase 1 and 2 enzymes which are essential for the synthesis of prostaglandins. The drug causes adverse effects in 30%-60% of users. A significant number of patients discontinued use of indomethacin due to intolerance to these side effects, mainly those involving the CNS and GI tract. Headaches, which may be accompanied by ataxia, tremor, dizziness or insomnia, are the most common CNS side effects. Reduction of the dose may reduce the intensity, but makes the drug less effective.

The GI tract adverse reactions include nausea with or without vomiting, indigestion, heartburn, gastric bleeding, ulcerations, flatulence, epigastric pain, gingival ulcers, diarrhea and gastroenteritis. These effects may be minimized when the drug is taken after a meal or with an antacid.

Phenylbutazone was introduced in 1949 for the treatment of rheumatoid arthritis. However, its use in humans has been discontinued due to its adverse reactions which include GI ulceration, aplastic anemia, gingival lesions, liver damage, especially when given with some analgesics, internal bleeding, epigastric distress, nausea, vomiting and suppression of white blood cell production. The drug is not marketed for human use. However, it is used in animals.

Ibuprofen was introduced into the European market in 1969 and into the U.S. in 1974. Its mechanism of action is identical to other NSAIDs and possesses analgesic, antipyretic and anti-inflammatory activity. It is used for relief of headache as well as in diseases such as

osteoarthritis, tendonitis, bursitis, gout and rheumatoid arthritis. Ibuprofen possesses side effects similar to those encountered with other NSAIDs. These adverse effects include dyspepsia, gastric irritation, diarrhea, constipation, dizziness and heart attacks if used in large doses and for prolonged periods of time. At lower doses of 1200 mg daily, ibuprofen has low incidence of GI tract side effects. The usual dose for gout is 400 – 800 mg three to four times daily until the gout attack has resolved.

Naproxen has similar mechanism of action, side effects and uses as ibuprofen. However, the plasma half-life of naproxen ranges from 10 to 20 hours while that of ibuprofen ranges from 2 to 4 hours. The usual dose for treating gout attacks is 750 mg one time followed by 250 mg 2 to 3 times daily until the attack subsides.

Prophylaxis

The purpose of treatment during the time when the patient is symptom-free is to reduce the frequency of recurrences and to prevent or minimize deposition of MSU tophi in the joints.

Colchicine is a drug that originally was extracted from the plant *Colchicum autumnale* (meadow saffron). In 2009 the FDA approved its use as monotherapy for treating acute gout flares and in the prevention of gout attacks. The precise mechanism of action is unknown. Moreover, it may be involved in lactic acid production by leukocytes, resulting in a decrease in uric acid deposition in the joints. The usual adult dose is 1.2 to 2.4 mg daily. For prophylaxis the recommended dose is 0.6 mg once or twice daily with a maximum dose of 1.2 mg/day. Colchicine is contraindicated in renal failure. Its toxicity is encountered when given along with antilipidemic drugs. Adverse effects include damage to bone marrow as a result of its inhibition of mitosis, vomiting, nausea, headache, epigastric pain and dizziness.

Probenecid is a drug that increases the rate of uric acid excretion from the blood by inhibiting its tubular reabsorption. Its adverse effects include headache, dizziness, dermatitis, pruritus, nausea, vomiting, anorexia, renal colic, and increased urinary frequency. Usually the initial adult dose is 250 mg twice daily for a week and then 500 mg twice daily. Dosage between attacks should be adjusted by reducing the intake of the medication by 500 mg every 6 months until uric acid blood level has normalized.

Sulfinpyrazone is a drug that lowers uric acid from the blood. It prevents gout attack but is of no value in treating an attack that has begun. The usual initial dose is 100 mg daily and gradually increases to 200 to 400 mg daily. Side effects include nausea, vomiting, loss of appetite, difficulty in breathing and headache. It is contraindicated in renal impairment or failure.

Pegloticase is a newer drug and is an enzyme that lowers uric acid blood level and thus reduces deposits of MSU crystals in the joints. The FDA approved its use for treatment of gout in 2010. The drug is a recombinant uricase which catalyzes the oxidation of uric acid. The drug can interact with other anti-gout medications such as allopurinol, probenecid, or febuxostat. Pegloticase is administered intravenously once every two weeks. Allergic reactions include hives, difficulty in breathing, light-headedness, tachycardia, irritation of the skin, wheezing and swelling of the lips. Other reactions include nausea, vomiting, constipation and stuffy nose.

Febuxostat is another newer drug and is a xanthine oxidase inhibitor that lowers the production of uric acid in the blood. It is used for the prevention of gout attacks but not to combat attacks already in progress. The drug was approved by the FDA in 2009 for the treatment

of hyperuricemia and chronic gout. Febuxostat has been shown to be more effective than allopurinol in reducing uric acid in the blood, but from a clinical point of view, the drug is not more efficacious. It is recommended for patients who cannot tolerate allopurinol. Side effects include nausea, vomiting, headache, skin rash, shortness of breath and increased liver enzyme levels. Febuxostat is administered orally in a daily dose of 40 or 80 mg before or after meals. The dose may be increased in accordance with the level of uric acid in the blood. The drug is available in tablets of 40 and 80 mg.

Allopurinol is a uric acid lowering drug that acts by inhibiting xanthine oxidase and is used in the prophylaxis of gout attacks, but not to relieve acute attacks. It is used mainly in patients experiencing uric acid overproduction, unresponsive patients to other uric lowering drugs, and patients with renal impairment, kidney or urinary stones. Side effects include hypersensitivity syndrome which is characterized by fever, skin rash, hepatitis, eosinophilia, toxic epidermal necrolysis and Steven-Johnson Syndrome. Other side effects include nausea, vomiting and drowsiness. The recommended daily dose is 200 to 400 mg.

SUMMARY

Gout is a common condition characterized by pain and tophi in the joints as a result of hyperuricemia. It can affect any joint in the body. There is no cure for gout, but it can be minimized by using medications that lower uric acid blood levels. To alleviate the pain associated with gout attacks, a number of medications, especially the NSAIDs, are used. Since purine, which is the main source of uric acid, is produced by the body and is found in the diet, drugs that increase uric acid excretion as well as avoidance of foods rich in purine, are beneficial.

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 Define "gout" & describe its characteristics YES NO
 List symptoms of gout YES NO
 Discuss drugs used to treat gout YES NO
 Describe side effects associated with gout drugs YES NO
 Comment upon MOAs of gout drugs YES NO

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| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
3. Relevance of topic
4. What did you like most about this lesson? _____
5. What did you like least about this lesson? _____

Please Mark the Correct Answer(s)

- | | |
|---|--|
| <p>1. Gout affects all joints, but mainly the base of the big toe.
 A. True B. False</p> <p>2. Which enzyme is absent in the human body?
 A. Xanthine oxidase
 B. Guanine deaminase
 C. Uricase
 D. Inosine</p> <p>3. Conversion of guanosine to guanine is catalyzed by:
 A. Hypoxanthinase
 B. Adenosine reductase
 C. Guanine deaminase
 D. Purine nucleoside phosphorylase</p> <p>4. A deposited crystal of MSU in a joint is known as a:
 A. Calculus
 B. Tophus
 C. Crystaluria
 D. Keratosis</p> <p>5. Which drug inhibits xanthine oxidase?
 A. Allopurinol
 B. Probenecid
 C. Pegloticase
 D. Colchicine</p> | <p>6. Which of these may trigger a gout attack?
 A. Diuretics
 B. Corticosteroids
 C. Antibiotics
 D. Sedatives</p> <p>7. Which of these is no longer indicated for human use?
 A. Indomethacin
 B. Febuxostat
 C. Sulfipyrazone
 D. Phenylbutazone</p> <p>8. Gout may be a hereditary disease.
 A. True B. False</p> <p>9. Which of these is administered via IV?
 A. Allopurinol
 B. Probenecid
 C. Pegloticase
 D. Febuxostat</p> <p>10. Which of these is not considered a risk factor of hyperuricemia?
 A. Age
 B. Obesity
 C. Diet
 D. Occupation</p> |
|---|--|

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