Clinical Review

Hyperuricemia and Gout

Richard W. Sloan, MD
Hershey, Pennsylvania

Although chronic tophaceous gout has become increasingly uncommon, hyperuricemia and acute gout are still common clinical entities. Most patients with hyperuricemia are underexcreters, and many of these cases are drug induced. Since longstanding asymptomatic hyperuricemia does not appear to cause progressive renal insufficiency, and uric acid renal stones are uncommon in underexcreters, these patients generally require no treatment. The minority of patients who overproduce uric acid are at increased risk for urolithiasis, and therapy should be decided on an individual basis. Acute gout is best treated with colchicine or indomethacin. The newer nonsteroidal anti-inflammatory drugs (ie, ibuprofen, sulindac) may prove to be equally effective and are associated with fewer gastrointestinal side effects. Prophylaxis should be undertaken in patients with recurrent gout or documented uric acid urolithiasis. Although uricosuric drugs appear to be less toxic than allopurinol, they should not be used in patients who overproduce uric acid or in patients who have a history of urolithiasis or renal insufficiency. The allopurinol hypersensitivity syndrome is being reported with increased frequency and may be fatal.

Uric Acid Metabolism

Uric acid is the end product of purine metabolism. Purines are derived from two general sources: dietary purines, and purines resulting from the normal metabolic turnover of cells. The total amount of urate in the body may vary widely among individuals. In an adult man on a purine-free diet, the average total body urate is 1200 mg. In women, the total urate pool may be only 50 percent of this value. In patients with chronic tophaceous gout, the total urate pool can exceed 25 gm. Since approximately 50 percent of the urate pool is turned over each day, an average man

From the Department of Family and Community Medicine, The Milton S. Hershey Medical Center, The Pennsylvania State University, Hershey, Pennsylvania. Requests for reprints should be addressed to Dr. Richard W. Sloan, The Pennsylvania State University, 500 University Drive, Hershey, PA 17033.

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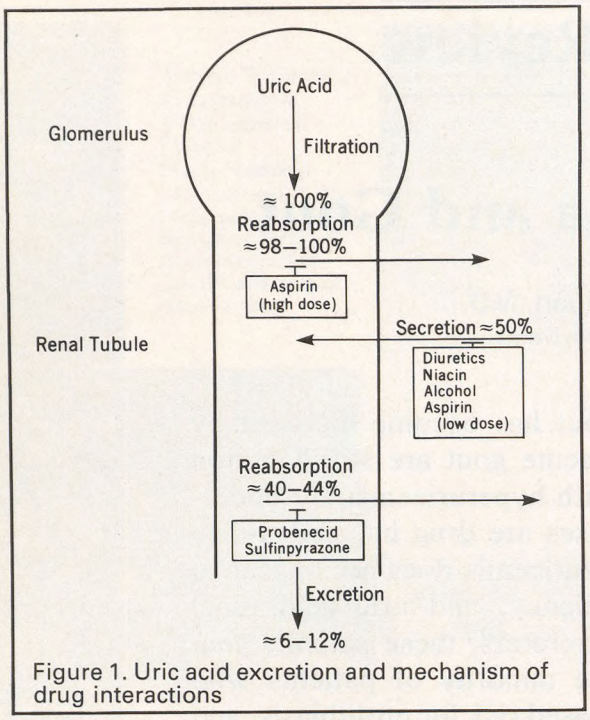

Figure 1. Uric acid excretion and mechanism of drug interactions

would excrete 600 mg of uric acid per day: two thirds of this amount is excreted in the urine, and one third is excreted in the feces.[1]

The renal handling of uric acid is rather complex, and some details are still controversial (Figure 1). Approximately 100 percent of the uric acid is filtered by the glomerulus, most of which is resorbed in the proximal tubule. Approximately 50 percent of the uric acid is then actively secreted back into the proximal tubule. Postsecretory resorption also occurs to a varying degree. The net amount of uric acid excreted in the urine depends on the balance between secretory and resorptive processes and averages 6 to 12 percent of the filtered load.[2]

Asymptomatic Hyperuricemia

Although hyperuricemia is usually diagnosed after several serum uric acid measurements are greater than 8.0 mg/100 mL in men or greater than 7.0 mg/100 mL in women, the normal values may vary among laboratories, according to methodology, and among study populations.[3]

Etiology

Although hyperuricemia may be primary with no identifiable cause, secondary causes should be sought and excluded. There are a number of drugs that may compete with uric acid for renal secretory sites and subsequently cause hyperuricemia (Table 1). Diuretics and aspirin are the most common drugs that cause a secondary hyperuricemia. All diuretics in common use have been associated with hyperuricemia except for spironolactone (Aldactone). Low-dose aspirin therapy (less than 2 g/d) is another common cause of secondary hyperuricemia. Ethyl alcohol, when used in excess, is also commonly associated with hyperuricemia and is thought to be caused by the lactic acidosis induced by alcohol; lactic acid competes with uric acid for renal secretory sites. Some alcoholic beverages also have a high purine content.

Hyperuricemia is common in a number of neoplastic disorders, including polycythemia vera, myeloid metaplasia, acute leukemia, and multiple myeloma. In these disorders, hyperuricemia is secondary to an increased production of uric acid secondary to the rapid turnover of neoplastic cells. Serum uric acid levels may increase rapidly when chemotherapy is instituted and cause the precipitation of uric acid crystals in the renal tubules, with subsequent acute renal failure. This complication may be prevented by treating these patients with allopurinol (Zyloprim). Other disease states associated with rapid turnover of cells, such as psoriasis and exfoliative dermatitis, can also cause hyperuricemia.

Heavy metals, such as lead, interfere with the ability of the proximal tubule to secrete uric acid, causing hyperuricemia as well as progressive renal insufficiency. A recent study of 44 patients with gout demonstrated that those patients with renal insufficiency had significantly elevated urinary lead concentrations after calcium disodium edetate (EDTA) mobilization.[4]

Genetically linked enzyme defects are an uncommon cause of hyperuricemia but have increased our understanding of primary hyperuricemia. These metabolic defects result in the overproduction of uric acid, associated with an increased rate of de novo purine biosynthesis. One such defect is hypoxanthine-guanine phosphoribosyl transferase (HPRT) deficiency, which occurs in the Lesch-Nyhan syndrome. In addition to

Table 1. Drugs That Interfere With Uric Acid Excretion

Decrease Uric Acid Excretion	Increase Uric Acid Excretion
Alcohol	Aspirin (high dose)
Diuretics	Probenecid
Nicotinic acid	Sulfinpyrazone
L-dopa	Phenylbutazone (high dose)
Ethambutol	
Aspirin (low dose)	
Phenylbutazone (low dose)	

hyperuricemia, this syndrome is characterized by mental and growth retardation, choreoathetosis, spasticity, and self-mutilating behavior. A second enzyme defect resulting in primary hyperuricemia is increased activity of phosphoribosylpyrophosphate (PRPP) synthetase.

Hypertension, obesity, hyperlipidemia, and diabetes mellitus are commonly associated with primary hyperuricemia and gout. Often these patients have a positive family history, and although the exact biochemical defect has not been elucidated, it is likely that these disorders are also under genetic control.

Diagnostic Evaluation

In evaluating a patient with hyperuricemia, a useful diagnostic study is the 24-hour urine test for uric acid. Before performing this test, a thorough drug history should be taken. Many drugs will alter the total amount of uric acid excreted in the urine per day (Table 1). Low-dose aspirin therapy may cause hyperuricemia and low 24-hour urine uric acid levels (less than 450 mg). A hyperuricemic patient on diuretic therapy may also be expected to have low 24-hour urine uric acid levels, and the 24-hour urine collection may not be helpful.

In general, the 24-hour urine for uric acid test allows the physician to determine the most appropriate therapy and to assess the risk of urolithiasis. Ideally, the test should be performed when the patient is on a purine-free diet. Foods high in purines include liver, sweetbreads, kidney, tripe, and other visceral meats. The patient should abstain from alcohol for 24 hours prior to the test and during the urine collection. The results of the 24-hour urine test will divide hyperuricemic patients into two general categories: overproducers (greater than 600 mg/d of uric acid), and underexcreters (less than 600 mg/d of uric acid). An outpatient on an ordinary diet with a 24-hour urine uric acid reading of greater than 1,000 mg/d is considered to be an overproducer.

Of all patients with hyperuricemia, approximately 25 percent are overproducers and 75 percent are underexcreters. Overproducers are at increased risk for urolithiasis. Another indicator of the risk of urolithiasis is the urine uric acid to creatinine ratio. If this ratio is greater than 1 to 1, the patient may be at increased risk for urolithiasis. Additional factors that increase the risk of uric acid urolithiasis are urine concentration and pH, since uric acid is more likely to crystallize in a highly concentrated acid urine.[5]

Treatment

The question of when to treat an asymptomatic hyperuricemic patient has been debated through the years. A decision to treat commits the patient to lifelong therapy. An acute attack of gouty arthritis, although painful, is readily treatable and tends to resolve completely. In the past the major reason given for treating asymptomatic hyperuricemia was to prevent uric acid-induced renal disease. Hyperuricemia was thought to cause three general types of renal disease: gouty nephropathy, intratubular crystallization of uric acid, and urolithiasis. Recent studies have cast considerable doubt on the existence of gouty nephropathy.[6-8] Patients with longstanding hyperuricemia do not appear to have any greater incidence of progressive renal failure than would a closely matched control group. Intratubular crystal deposition continues to be a well-recognized complication of chemotherapy in patients with certain neoplastic disorders and can lead to acute renal failure. This complication can be prevented with allopurinol therapy. Urolithiasis also continues to be a well-recognized complication of hyperuricemia and is most common in overproducers and in patients with a highly concentrated acid urine. If untreated, the resulting obstruction and infection from recurrent urolithiasis can cause significant irreversible renal damage.

In the family practice setting, a significant number of patients with asymptomatic hyperuricemia

receive thiazide diuretics for the treatment of hypertension. The overwhelming majority of these patients would be expected to be underexcreters and therefore at low risk for urolithiasis. Generally, no treatment is required unless the serum uric acid is persistently greater than 13 mg/100 mL in men or 10 mg/100 mL in women.[9] The patient should be encouraged to maintain an adequate fluid intake. An acceptable method of lowering the serum uric acid in this clinical situation is to reduce the dose of the diuretic. In treating hypertension with hydrochlorthiazide, the ceiling effect occurs at approximately 100 mg/d; however, most of the therapeutic effect is seen with doses up to 50 mg/d, and progressively smaller increments of blood pressure reduction occur as the dose is increased from 50 to 100 mg/d. On the other hand, the higher dose will significantly potentiate hypokalemia and hyperuricemia.[10,11]

Asymptomatic hyperuricemic patients who are not receiving diuretic therapy or other drugs that alter uric acid excretion should be evaluated with a 24-hour urine collection for uric acid. Once again, most of these patients will be underexcreters and require no treatment unless the serum uric acid is persistently greater than 13 mg/100 mL in men or 10 mg/100 mL in women.

A few patients will be determined to be overproducers. These patients are at increased risk for urolithiasis, especially if the 24-hour urine test for uric acid is greater than 1000 mg. Initially therapy can be directed at dietary manipulation and increased fluid intake. Alkalinization of the urine is not practical on a long-term basis. If these measures are unsuccessful or if the patient becomes symptomatic with acute gout or renal colic, long-term allopurinol therapy should be considered after treatment of the acute episode. Uricosuric drugs are contraindicated in overproducers.

Acute Gouty Arthritis

Clinical Presentation

Acute gouty arthritis usually occurs in men in their fourth and fifth decades of life. The disease is uncommon in premenopausal women. Classically, acute attacks of gout occur in peripheral joints, and the joint most commonly involved is the first metatarsophalangeal joint (podagra). Podagra is the initial manifestation of gout in over 50 percent of patients. Although usually only one joint is involved, a few patients may experience an acute attack involving several joints. The pain comes on suddenly and the joint is exquisitely tender; the weight of a bed sheet will be unbearable. Without treatment, the attack tends to resolve in three to ten days, leaving no residual abnormalities. Attacks tend to recur at more frequent intervals and with increased severity and duration. Ultimately, the patient may develop disfiguring gouty tophi, irreversible joint destruction, and progressive disability.

Pathophysiology

An acute attack of gouty arthritis is initiated when monosodium urate crystals precipitate out of solution in the synovial fluid. The propensity of gout to affect the peripheral joints in the lower extremities may be related to reduced body temperatures in these joints, which further reduces the solubility of the crystals. The tremendous pressure and trauma to which these joints are exposed may lead to degenerative changes and joint effusions, which are contributing factors. The irregular surface properties of urate crystals appear to be important for initiating an inflammatory response. Chemotactic stimuli attract neutrophils to the synovial space. The inflammatory response is intensified by various mediators that cause vasodilation, increased vessel permeability, and recruitment of additional neutrophils. As the neutrophils attempt to phagocytize the needle-shaped crystals, many undergo cell lysis and release of lysosomal enzymes, which further potentiates the inflammatory response. Eventually the urate crystals are digested and the reaction subsides.[12]

Diagnosis

The diagnosis of acute gouty arthritis can be confirmed by aspirating the affected joint and demonstrating the presence of monosodium urate crystals. Monosodium urate crystals have a typical needle-shaped appearance and are strongly negatively birefringent when examined under the polarized microscope. Frequently crystals will be seen within the cytoplasm of neutrophils following phagocytosis.

Sometimes it is not practical or possible to obtain synovial fluid for analysis. In this case, acute gouty arthritis can be strongly suspected in a male patient (or postmenopausal female patient) with

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typical monoarticular arthritis, an elevated serum uric acid level, and a prompt response to colchicine therapy. Although this triad is 90 percent specific, other rheumatologic conditions, such as sarcoid arthritis and pseudogout, may also respond to colchicine therapy.[13]

Treatment

Colchicine has been used in the treatment of acute gout for many years. The drug is a cytotoxin which interferes with mitotic spindles and other cellular functions that depend on normal microtubule function. Cells undergoing mitosis are arrested in metaphase in the presence of colchicine. Colchicine interferes with the normal mobility and phagocytic function of neutrophils. It is hypothesized that the drug's efficacy in the treatment of acute gout is related to its ability to inhibit the normal migration of neutrophils and prevent the phagocytosis of urate crystals.

When used to treat acute gout, colchicine may be given either orally or intravenously. When given orally, the usual dose is 0.5 mg repeated every hour until symptoms subside or diarrhea develops. The maximum dose is 4 to 6 mg. For patients with significant hepatic or renal insufficiency, lower doses should be given. The most common and earliest side effects of colchicine therapy involve the gastrointestinal tract. Nausea, vomiting, abdominal pain, and profuse diarrhea predictably develop with increasing dosage. In elderly patients the diarrhea may become quite severe and hemorrhagic and produce significant electrolyte imbalance. Colchicine suppresses hematopoiesis and causes leukopenia, and other more severe blood dyscrasias have been reported. When given in very large doses, colchicine produces muscle weakness and respiratory depression.

Colchicine may be given intravenously and produces an even more dramatic response in acute gout when given by this route. Symptomatic relief usually occurs within six hours, and the patient may be totally asymptomatic after 24 hours. A major advantage of giving colchicine intravenously is that gastrointestinal toxicity is avoided. However, extravasation of the colchicine solution can cause severe necrosis of surrounding tissues. The usual dose is 2 mg of colchicine solution diluted in 20 mL of normal saline infused slowly. A second dose of 1 mg may be given six hours later. The total intravenous dose should not exceed 4 mg. The dose should be reduced for patients with renal or hepatic insufficiency. Intravenous colchicine is more likely than oral therapy to cause leukopenia.

Indomethacin is a very effective drug for the treatment of acute gouty arthritis and is an excellent alternative to colchicine. As with other nonsteroidal anti-inflammatory drugs, the efficacy of indomethacin appears to be related to inhibition of prostaglandin biosynthesis.[14] The usual dose ranges from 100 to 200 mg/d given in three to four divided doses; doses in the upper portion of this range are generally prescribed during the first 24 hours of treatment. The most common side effects of indomethacin therapy involve the gastrointestinal tract and central nervous system.[15] Gastrointestinal tract side effects range from indigestion, nausea, and epigastric discomfort to gastritis, gastric ulceration, and hemorrhage. The drug is contraindicated in patients with peptic ulcer disease and should be prescribed with food or antacids in all patients. When the total daily dose exceeds 100 mg, central nervous system side effects are quite common and include headache, confusion, disorientation, dizziness, hallucinations, and (rarely) seizures. Since renin release appears to be mediated by prostaglandins, susceptible individuals can develop a hyporeninemic state when treated with prostaglandin inhibitors such as indomethacin. This can lead to hypoaldosteronism and subsequent hyperkalemia.[16-18] Cornea deposits and toxic hepatitis are rare complications of indomethacin therapy.

Phenylbutazone is equal in effectiveness to indomethacin but is potentially more toxic. Initial doses in the range of 400 to 600 mg/d are generally prescribed and tapered over a period of seven days. Like indomethacin, phenylbutazone has significant gastrointestinal toxicity and should be prescribed with food or antacids. The drug is contraindicated in patients with peptic ulcer disease. Phenylbutazone causes significant salt and water retention, which can be a problem in patients with hypertension or congestive heart failure. Phenylbutazone has been implicated in a number of blood dyscrasias, including aplastic anemia, agranulocytosis, leukopenia, and thrombocytopenia, some of which have been fatal.[19] Agranulocytosis

is usually an idiosyncratic response occurring predominantly in younger patients, whereas aplastic anemia is usually dose related and occurs predominantly in older patients. Serious blood dyscrasias are unlikely when therapy is limited to seven days or less. Phenylbutazone is highly bound to serum albumin and can displace warfarin from binding sites, with resultant increased anticoagulant effect.

Several of the newer nonsteroidal anti-inflammatory drugs (ie, ibuprofen, naproxen, and sulindac) have been shown to be effective in the treatment of acute gout.[14,20] To be effective, these drugs should be given in their maximum recommended dose. Since ibuprofen and sulindac have a lower incidence of gastrointestinal toxicity, they may be advantageous in a patient with a history of peptic ulcer disease or gastrointestinal bleeding.

Prophylaxis

Prophylactic therapy should be considered in patients with recurrent attacks of acute gout or in patients with uric acid renal stones. Any patient started on chronic prophylactic therapy is at increased risk for developing an acute attack of gout. This phenomena is related to the mobilization of uric acid stores; any sudden changes in serum uric acid concentration (either increase or decrease) may precipitate an acute attack. For this reason, when initiating chronic prophylactic therapy, colchicine in low doses (0.5 mg twice daily) should be coadministered. The low-dose colchicine should be continued until dosage titrations have ceased and the serum uric acid has been stable for three consecutive weeks.

Nondrug modalities of therapy should be discussed with the patient. Dietary moderation and weight reduction to ideal body weight are important factors. Adherence to a low-purine diet can reduce serum uric acid by 1 mg/100 mL, but patient compliance is low. Abstinence from alcohol will also significantly lower serum uric acid levels.

Allopurinol is the drug of choice in overproducers and in patients with renal insufficiency or a history of renal stones. The drug inhibits xanthine oxidase, an enzyme necessary for the final steps in the biosynthesis of uric acid. The drug is well absorbed from the gastrointestinal tract following oral administration. An active metabolite, oxipurinol, has a long half-life (28 hours), which allows allopurinol to be given in a single daily dose. The usual starting dose is 100 mg/d. This dose is increased by 100 mg each week until the serum uric acid has decreased to within the normal range. The average daily dose is 300 mg, but occasional patients may require doses up to 900 mg/d. Oxipurinol is predominantly eliminated by the kidney; therefore, the dose of allopurinol must be reduced in patients with significant renal insufficiency. Allopurinol is generally a well-tolerated drug; however, it is probably more toxic than the standard uricosuric drugs (probenecid and sulfinpyrazone). The most common side effects are gastrointestinal upset and hypersensitivity reactions.

Allopurinol hypersensitivity reactions have been reported with increasing frequency during the last five years.[21] Ten fatalities resulting from complications of allopurinol hypersensitivity have been reported. Failure to reduce the dose of the drug in a patient with renal insufficiency appears to increase the likelihood of this syndrome. The average time to onset of symptoms is three to four weeks after instituting therapy. Systemic signs and symptoms include fever, chills, myalgia, arthralgias, and malaise. Eosinophilia is a common laboratory finding. Most patients exhibit a prominent cutaneous reaction, which ranges from a diffuse maculopapular rash to toxic epidermal necrolysis and Stevens-Johnson syndrome.[21-23] The incidence of a rash is increased significantly when ampicillin is coadministered with allopurinol.[24] The vasculitis associated with the allopurinol hypersensitivity syndrome can also cause acute renal failure, hepatitis, and seizures.[25-27]

Allopurinol is involved in several important drug interactions. The dose of the chemotherapeutic drugs, 6-mercaptopurine and azathioprine, must be significantly reduced when coadministered with allopurinol. Allopurinol can inhibit the liver microsomal enzyme system and prolong the half-life of drugs requiring this system for metabolism (eg, warfarin). Prothrombin times should be followed closely in anticoagulated patients started on allopurinol, and low anticoagulant doses should be anticipated.

Uricosuric drugs continue to be useful agents in the prophylactic therapy of recurrent gout. The drugs (probenecid and sulfinpyrazone) are ineffective in patients with renal insufficiency and

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contraindicated in overproducers and patients with a history of renal stones. Some clinicians have suggested that uricosuric drugs no longer have a place in the prophylactic treatment of recurrent gout because of the possibility of renal stone formation.[28] The incidence of renal stones in properly selected patients, however, is low and the potential for serious toxic reactions is probably less than with allopurinol.

Probenecid (Benemid) is the prototype uricosuric drug; it blocks the resorption of uric acid, which increases the amount excreted in the urine. This action is nullified when aspirin is coadministered with probenecid. Because of the risk of renal stone formation, probenecid should be started in a low dose and titrated upward. The patient should be instructed to increase fluid intake. Alkalinization of the urine (pH greater than 6.0) is rarely necessary and impractical on a long-term basis. The usual starting dose is 250 mg twice a day. This is gradually increased to an average maintenance dose of between 1.0 to 1.5 g/d. Probenecid is a well-tolerated drug and major toxicity is quite rate. The most common side effects are gastrointestinal upset and hypersensitivity reactions. Probenecid increases the blood levels and prolongs the half-life of penicillins and cephalosporins.

Sulfinpyrazone is a congener of phenylbutazone but is not nearly so toxic. The drug is three to six times more potent than probenecid in uricosuric activity and effectively blocks the resorption of uric acid, increasing the amount of uric acid excreted in the urine. The usual starting dose is 50 mg twice a day. This is gradually increased to a maintenance dose that averages between 200 mg and 800 mg daily in three to four divided doses. The drug is well tolerated, and significant side effects are rare. In addition to being a potent uricosuric drug, sulfinpyrazone (Anturane) also has antiplatelet properties. No serious adverse effects, including renal calculi, were reported in the 580 patients receiving sulfinpyrazone (800 mg/d) during the Anturane reinfarction trial.[29]

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