Newer Therapy for Hyperuricemia

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Uric acid is one intermediate product of purine metabolism. Since the development of higher primates millions of years ago, humans are unable to catabolize uric acid, which leads to the presence of uric acid in the body because, in contrast to lower class animals, humans lack the enzymes - uricase, allantoinase, allantoicase and urease - which convert uric acid into allantoin, allantaoic acid, urea, ammonia and carbon dioxide, respectively.

Hyperuricemia, a value of serum uric acid of over 7.0 mg/dL, is a common medical condition. It can result from (1) abnormalities in enzymes that control uric acid synthesis (5-phosphoribosyl-1-pyrophosphate synthetase over-activity or deficiency in hypoxanthine-guanine- phosphoribosyl transferase), (2) disorders that lead to over production of uric acid (myeloproliferative disorders, hypoxemia, glycosgenosis, etc.), (3) drugs or substances that lead to over production of uric acid (alcohol, warfarin, cytotoxic drugs, nicotinic acid), (4) disorders that lead to decreased renal uric acid excretion (renal failure, dehydration, lead intoxication, starvation, acidosis, hyperparathyroidism, hypothyroidism, etc.), and (5) drugs or substances that decrease renal uric acid excretion (alcohol, diuretics, low dose aspirin, ethambutol, pyrazinamide, cyclosporine, etc.).

Hyperuricemia per se is generally asymptomatic. However, in certain conditions, acute hyperuricemia such as that seen in acute tumor lysis syndrome can cause acute renal failure by obstruction of renal tubules by uric acid crystals. In contrast, chronic hyperuricemia, monosodium urate crystals (crystals formed by sodium and urate ion) deposition, can occur in various tissues of the body, leading to the development of gout and urate nephropathy. Over-excretion of uric acid in the urine (over 1,000 mg/day) increases the risk of urinary uric acid stone development. Recently, hyperuricemia has been proposed as a risk factor for the development of ischemic heart disease.

In treating a patient with hyperuricemia, the physician should answer the following questions: 1. Does the patient have true and sustained hyperuricemia? 2. What is the cause of hyperuricemia and can it be corrected? 3. Are there any complications of hyperuricemia (acute arthritis or gout, or renal calculi)? 4. Does the patient require treatment, and if so, what is the drug of choice?

Management of hyperuricemia requires both non-pharmacologic and pharmacologic means. The non-pharmacologic means include correction of conditions that can cause hyperuricemia, e.g. hypoxemia, dehydration or alcohol consumption. Drugs that can cause hyperuricemia should be discontinued, if possible. Tight dietary restriction is not necessary, as it can slightly decrease serum uric acid. A recent recommendation is life-style modification, which includes weight reduction to the ideal body weight, restriction of alcohol consumption (especially beer), and limited consumption of food with high purine contents. A balanced diet of 1,600 Kcal/day, with 40% derived from carbohydrate, 30% from protein and 30% from fat can decrease serum uric acid to approximately 18% of its original level.

Uricosuric agents, including probenecid, sulfinpyrazone and benzbromarone, were introduced onto the market in the 1950s, and have been shown to effectively decrease serum uric acid. These agents work by inhibiting uric reabsorption at the proximal renal tubules at the URAT1 transporter site. However, these drugs are not effective in a patient with impaired renal function (creatinine clearance < 80 ml/min for probenecid, and < 30 ml/min for benzbromarone and sulfinpyrazone), and for approximately 25% of the patient's, adequate control of hyperuricemia cannot be achieved. Unfortunately, hepatotoxicity of benzbro marone is a major concern in many countries. These agents are contraindicated in patients with a history of renal calculi, or who have urinary uric acid excretion > 1,000 mg/day. Azapropazone and phenylbutazone are non-steroidal anti-inflammatory drugs that have a moderate uricosuric property. However, long term use of these agents is associated with upper gastrointestinal bleeding and perforations, and is not recommend for use in the treatment of hyperuricemia.

The development of allopurinol in the late 1950s led to a major advance in the treatment of hyperuricemia. It inhibits xanthine oxidase, a key enzyme that metabolizes hypoxanthin to xanthine, and xanthine to uric acid. It has been shown to effectively reduce serum uric acid, and can be used in patients with renal calculi, over-excretion of uric acid in the urine or renal insufficiency (providing the dose is adjusted according to the creatinine clearance - as allopurinol and its metabolite are excreted primarily by the kidney). However, allopurinol hypersensitivity syndrome, with a high mortality rate, is a major concern when using this agent. Moreover, in many patients it cannot achieve the target hypouricemic level (< 6.0 mg/dL) by dose adjustment according to the creatinine clearance. Oxipurinol, the active metabolite of allopurinol, is only...
available in some countries, and has been shown to be as effective as allopurinol in reducing serum uric acid. It has an advantage over allopurinol in that it can be used in patients with an allergy to sulfa compounds, and does not exhibit cross reactivity with allopurinol.7

The limitation in the efficacy of uricosuric agents and allopurinol has led to the development of newer compounds for treating hyperuricemia. Febuxostat, a new class of non purine xanthine oxidase inhibitor that is more selective to xanthine oxidase than allopurinol, has recently been introduced to the market. In contrast to allopurinol, febuxostat and its metabolites have little dependence on renal excretion. In clinical trials, febuxostat has been shown to effectively decrease serum uric acid to the target level, and it can be used safely in patients with mild to moderate renal impairment.9 As humans lack the enzyme uricase, an enzyme that oxidizes uric acid to allantoin, for the synthesis of uricase for treating hyperuricemia has now been developed. Rasburicase, a natural uricase purified from Aspergillus flavus, has been developed and approved in treating hyperuricemia associated with tumor lysis syndrome. However, the development of autoantibodies to rasburicase has been found in approximately 10% of cases. Moreover, anaphylaxis, methemoglobinemia, and hemolysis in those with glucose-6-phosphate dehydrogenase deficiency, neutropenia and sepsis are a major concern.10,11 Another uricase from Candida utilis, formulated with polyethylene glycol (PEG uricase), has shown that a decrease in its antigenic prolongs its half life.12,13 Both uricas have been shown to effectively reduce serum uric acid and resolution of the tophi. More clinical studies on these two agents are ongoing.

Some other agents that are used for the treatment of cardiovascular disease that have modest uricosuric effects. Losartan, amlodipine and fenofibrate have been shown to have uricosuric effects.14,16 These agents might be useful in the difficult management of gout.

In conclusion, there has been some progression in the treatment of hyperuricemia. The newer and more potent hypouricemic agents are currently being developed. This should help to create better treatment for difficult cases of hyperuricemia in the future.

REFERENCES

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