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Treatment of gout and urate calculi with allopurinol

Report of Three Representative Cases

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ALLOPURINOL is a potent inhibitor of the enzyme xanthine oxidase; it is an isomer of hypoxanthine, the carbon and nitrogen atoms at the seventh and eighth positions of the purine ring being exchanged. The action of allopurinol is twofold, as an inhibitor and also as a substrate for xanthine oxidase. Since uric acid is formed by the action of xanthine oxidase on xanthine and hypoxanthine (*Fig. 1*), it follows that inhibition of the enzyme xanthine oxidase results in the formation of less than normal amounts of uric acid. As a result, purine end products are excreted in the three forms: hypoxanthine, xanthine, and uric acid.

The effect of allopurinol in lowering the concentrations of uric acid in serum and in urine was discovered fortuitously by Rundles and associates,[1] who sought xanthine oxidase inhibitors to slow the degradation of 6-mercaptopurine (6-MP). As a result of the blockage of xanthine oxidase, the conversion of 6-MP to thiouric acid is reduced, and the cytotoxic and immunosuppressive effects of 6-MP and other 6-substituted purines are enhanced several fold.[2] However, it is not in the field of antitumor therapy that allopurinol has been primarily useful, but rather in its ability to decrease the production of uric acid.[3]

In a continuing study, now in its third year, we are following the progress of 20 patients' disorders of uric acid metabolism whose case data we have previously reported.[4] These patients were initially selected from a larger group treated with allopurinol for two reasons: firstly, the patients had unusually severe gout, and secondly, all were available for prolonged study.

Patients in the Series

Fifteen patients with primary gout had an average duration of disease of nine years. The yearly average frequency of episodes in the years preceding the study was 6.5 per patient. Two patients had tophaceous deposits. All patients but two had had previous uricosuric therapy, but for various reasons the gout was not being adequately controlled. Six patients had uric

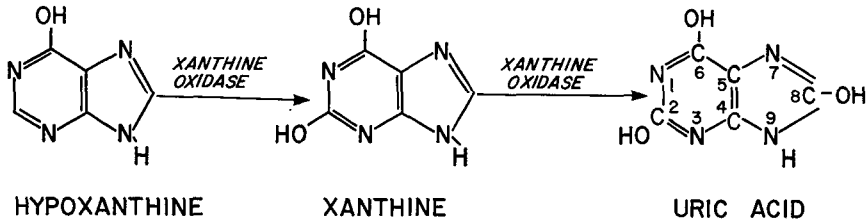

Fig. 1. Schematic sketch of chemical action of xanthine oxidase, which catabolizes the last two steps of purine degradation.

acid calculi, and as a group in the year before treatment had experienced a total of 20 bouts of uric acid stone. One patient with secondary hyperuricemia was included in the study.

Methods

Serum and urine content of uric acid was measured by the Bittner and associates' [5] cupric phenanthroline method using a Technicon AutoAnalyzer. By this method, the upper limit of normal for serum uric acid content in men and women is 7 mg and 6.5 mg per 100 ml, respectively. Without dietary purine restriction, the 24-hr uric acid excretion normally is less than 600 mg.

Results

Except for two patients who died of chronic renal disease during the study, the length of follow-up ranged from 22 to 34 months, and averaged 26 months. The average daily dose of allopurinol taken by the patients with gout was 350 mg. Although 13 of the 15 patients with gout had been treated earlier with uricosuric drugs, in only the two patients who had tophi was uricosuric therapy continued in the initial months of study. Eleven patients were given colchicine prophylactically in the first six months. The four patients not taking colchicine had a higher rate of gouty episodes. *Figure 2* is a graph showing the frequency of episodes of gout in the first two years, and indicates a remarkable decline that is being maintained. In the six months at the end of the second year of treatment only two attacks of gout occurred before treatment. The average serum uric acid content in the patients with gout was 9.4 mg per 100 ml; after treatment the average serum uric acid level is being steadily maintained at 6 mg per 100 ml (*Fig. 3*). The hands of a patient with tophaceous gout (*Fig. 4*, left) that failed to respond to 300 mg of sulfinpyrazone daily, were cleared of tophi (*Fig. 4*, right) after allopurinol, 300 mg daily was added to the therapy. Two of the six patients with uric acid lithiasis passed stones after administration of allopurinol was begun, in each case within six months of starting treatment. By comparison, 21 episodes of stone had been noted in the year preceding the onset of treat-

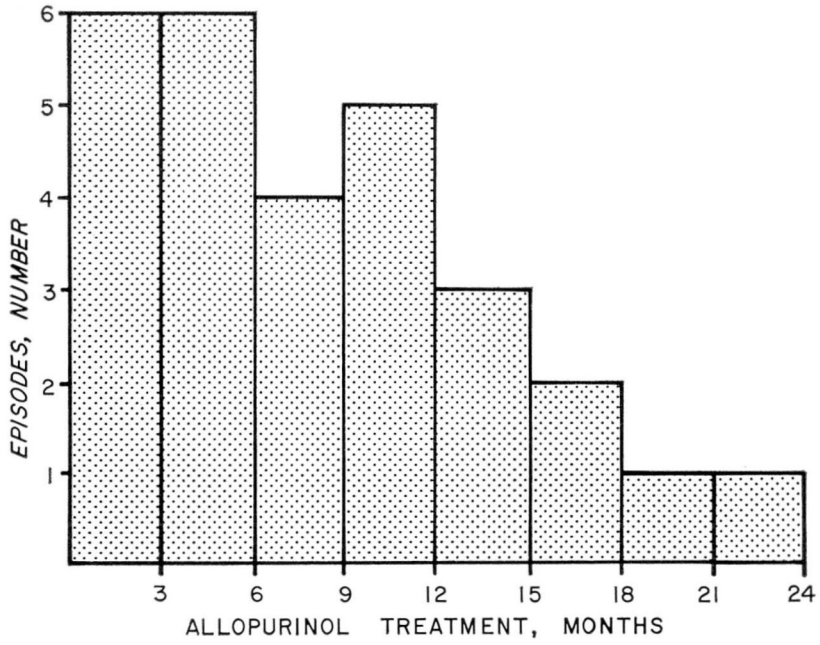

Fig. 2. Graph showing the steady decrease in attack rate of gout in 15 patients. (From O'Duffy, J. D., and Scherbel, A. L.: Allopurinol in the treatment of gout and urate calculi, Proceedings of the IV Panamerican Congress of Rheumatology, Mexico, *Excerpta Med. Found.*: in press; by permission of Excerpta Medica Foundation.)

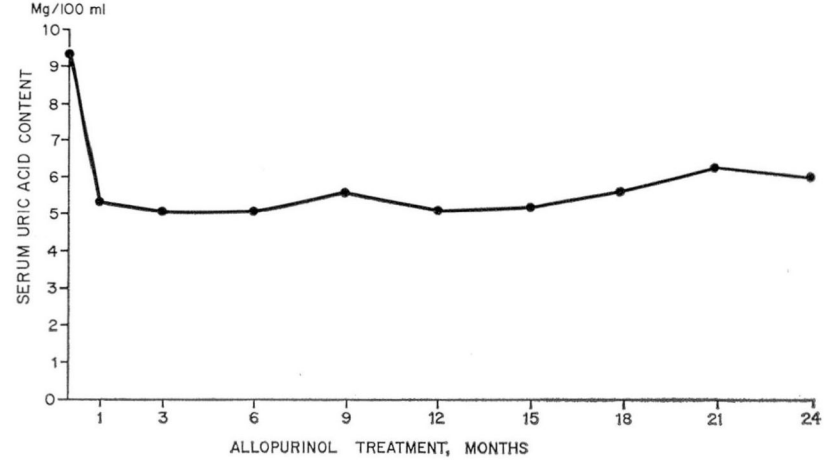

Fig. 3. Graph showing changes in serum uric acid content of 15 patients. The initial average serum uric acid level was 9.4 mg per 100 ml. With a course of allopurinol averaging 350 mg per day, the serum uric acid level is being maintained at the average of 6.0 mg per 100 ml. (From O'Duffy, J. D., and Scherbel, A. L.: Allopurinol in the treatment of gout and urate calculi, Proceedings of the IV Panamerican Congress of Rheumatology, Mexico, *Excerpta Med. Found.*: in press; by permission of Excerpta Medica Foundation.)

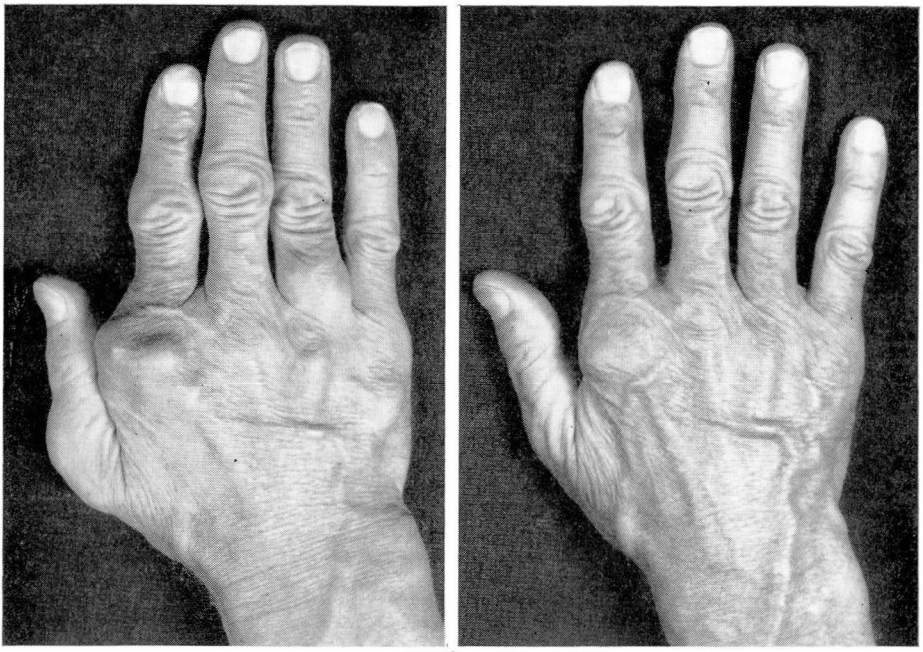

Fig. 4. Photographs showing that tophi at start of treatment (*left*) have disappeared after 20 months (*right*) of allopurinol therapy. (From O'Duffy, J. D., and Scherbel, A. L.: Allopurinol in the treatment of gout and urate calculi, Proceedings of the IV Panamerican Congress of Rheumatology, Mexico, *Excerpta Med. Found.*: in press; by permission of Excerpta Medica Foundation.)

ment (*Fig. 5*). Because uric acid calculi are radiolucent and often are overlooked in intravenous urograms, it is possible that the two calculi were present at the onset of therapy.

Comment. Although the concomitant use of an alkalinizing solution resulted in the dissolution of large preformed calculi in two patients, one of which is shown in *Figure 6,* in another patient, who was given only allopurinol without alkali, the urate renal stone persisted. The rate of decrease in the daily urinary excretion of uric acid is shown in *Figure 7.* The gradual slope of the curve was due to increasing dosage of allopurinol, and it was necessary to use an average daily dose of 520 mg to maintain a daily excretion of less than 500 mg.

Report of Three Representative Cases*

Case 1. A 45-year-old man with an ileostomy had passed showers of uric acid stones and gravel monthly after a colectomy performed for ulcerative colitis 10 years previously. Before

* *Case data are reported in reference 4.*

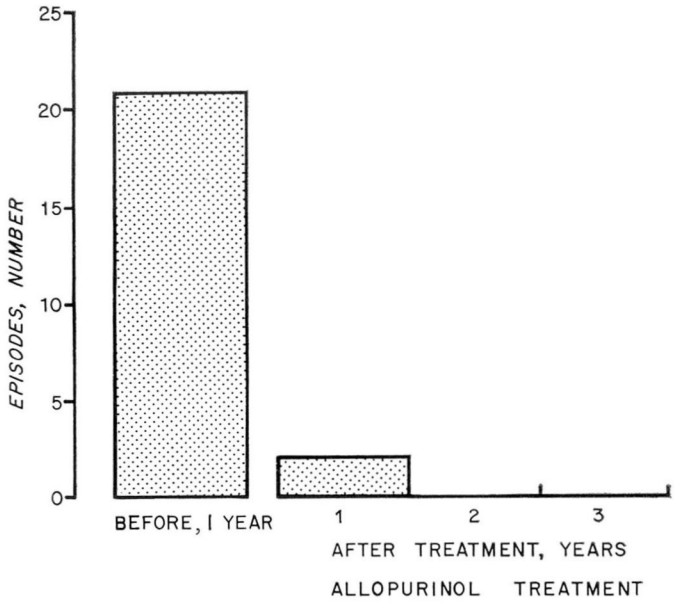

Fig. 5. Twenty-one attacks of uric stone occurred in the year before treatment with allopurinol. Two early attacks only, occurred during the entire period of treatment. (From O'Duffy, J. D., and Scherbel, A. L.: Allopurinol in the treatment of gout and urate calculi, Proceedings of the IV Panamerican Congress of Rheumatology, Mexico, *Excerpta Med. Found.*: in press; by permission of Excerpta Medica Foundation.)

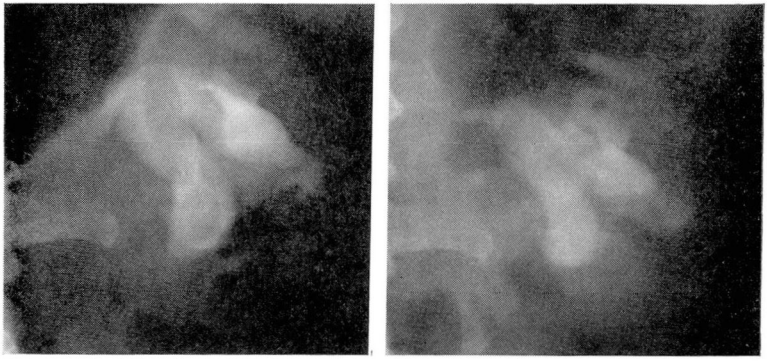

Fig. 6. Roentgenograms showing that a large radiolucent defect of a uric acid stone (*left*) disappeared (*right*) after 15 months of allopurinol therapy and urinary alkalinization. (From O'Duffy, J. D., and Scherbel, A. L.: Allopurinol in the treatment of gout and urate calculi, Proceedings of the IV Panamerican Congress of Rheumatology, Mexico, *Excerpta Med. Found.*: in press; by permission of Excerpta Medica Foundation.)

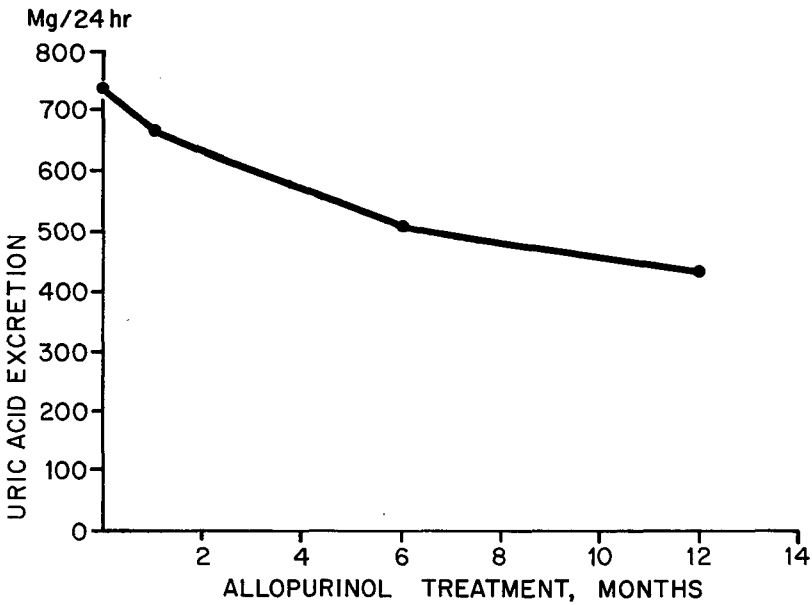

Fig. 7. Graph showing the gradual decline in the urinary excretion of uric acid with increasing dosage of allopurinol. The maintenance dosage was 520 mg per day. (From O'Duffy, J. D., and Scherbel, A. L.: Allopurinol in the treatment of gout and urate calculi, Proceedings of the IV Panamerican Congress of Rheumatology, Mexico, *Excerpta Med. Found.*: in press; by permission of Excerpta Medica Foundation.)

treatment with allopurinol, urinary excretion of uric acid was 1,100 mg daily. The patient passed a stone during the course of treatment with 300 mg of allopurinol daily, but since the dosage was increased to 600 mg daily to maintain a daily excretion of uric acid of less than 500 mg, he has experienced no further attacks in more than three years of treatment.

Case 2. A 45-year-old man had had recurrent gouty arthritis for five years. During an attack in a knee joint, urate crystals were seen in the synovial fluid. In the fifth year of gout, a nephrotic syndrome, with edema of the legs, and proteinuria developed. Daily protein excretion increased from 1.7 to 3.1 g. In February 1965, a 12-hr urine specimen revealed 90,000 casts, 10 million erythrocytes, and 40,000 leukocytes. Serum albumin was 2.4 g per 100 ml. A percutaneous renal biopsy showed no specific glomerular change according to light microscopy. While the patient was taking probenecid, 1.5 g daily, the serum uric acid content decreased from 9.8 mg to 5 mg per 100 ml, but episodes of gout continued. In May 1965, 400 mg of allopurinol daily was added, and excellent supression of joint symptoms ensued. However, proteinuria and cylindruria continued, and creatinine clearance decreased, from 118 ml per minute per 1.73 m^2 to 39 ml per minute, between January 1965 and February 1966. Probenecid was discontinued from the treatment in December 1965. In March 1967, creatinine clearance was 64 ml per minute per 1.73 m^2, and 24-hr urinary protein excretion had decreased to 0.25 g. By November 1967, creatinine clearance was 85 ml per minute; 24-hr protein excretion was 0.11 g; and no casts were seen. The blood pressure remained normal.

Comment. Albuminuria and reduction in glomerular filtration are early signs of renal involvement by gouty nephropathy. However, a nephrotic syndrome due to gout must be uncommon because it is not mentioned by Talbott[6] in his monograph on gout. In the patient in case 2, the improve-

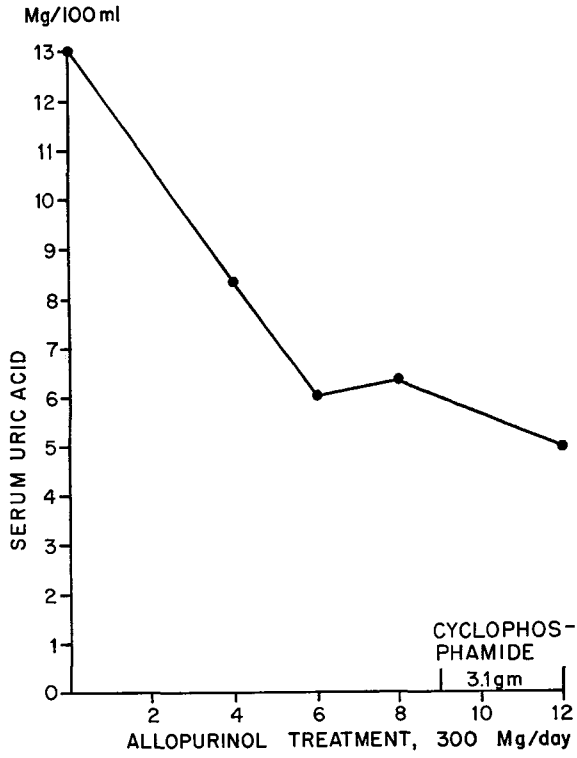

Fig. 8. Despite large doses of a cytotoxic drug, the lowered level of serum uric acid was maintained. (From O'Duffy, J. D., and Scherbel, A. L.: Allopurinol in the treatment of gout and urate calculi, Proceedings of the IV Panamerican Congress of Rheumatology, Mexico, *Excerpta Med. Found.*: in press; by permission of Excerpta Medica Foundation.)

ment in glomerular filtration appeared only after the administration of probenecid was discontinued. In addition, the urinary sediment returned to normal 18 months after a course of allopurinol was started. It is known that allopurinol does not affect established severe gouty renal disease, but it has been postulated that it might reverse early gouty nephropathy.[1] We believe that the early gouty nephropathy in the patient we treated was reversed by allopurinol. The mechanism may lie in the ability of the drug to reduce the filtered load of uric acid, an advantage not shared by the uricosuric agents.

Case 3. The course of a patient with lymphosarcoma and base line serum uric acid content of 13 mg per 100 ml is shown in *Figure 8*. It was feared that intravenous cyclophosphamide* would cause uric acid nephropathy. Daily treatment with 300 mg of allopurinol resulted in normal serum uric acid content, which was maintained when 3.1 g of cyclophosphamide was given intravenously.

* *Cytoxan, Mead Johnson Laboratories.*

Discussion

Although the uricosuric agents, probenecid and sulfinpyrazone, are generally effective in lowering serum content of uric acid, there are limitations to their use.[7] These agents are often ineffectual in the presence of decreased renal function, and in gouty persons with great overproduction of uric acid. Furthermore, since uricosuric agents increase the urinary excretion of uric acid they add to the hazards of urolithiasis. Even without treatment, patients with primary gout have a 12 to 18 percent incidence of uric acid stone, and, in secondary gout, stones may occur in 40 percent of patients.[8] Another disadvantage to the use of uricosuric drugs is their frequent ineffectiveness in chronic renal failure, in secondary gout, and when combined with salicylates. In contrast, allopurinol is effective in reducing serum uric acid content even in chronic renal failure,[9] and in secondary gout.[10]

In our own study, no reduced effectiveness of allopurinol was noted in two uremic patients nor in patients taking salicylates and thiazide antihypertensive agents. The usual treatment of uric acid urolithiasis by maintaining an alkaline urine through the administration of sodium and potassium citrate salts and high fluid intake is often successful. However, patients generally find these substances unpalatable, and often fail to continue their use. The hazards of excessive sodium ingestion are avoided when allopurinol is used.

At present we use urinary alkalinization only to dissolve preformed urate calculi, and maintain treatment with allopurinol thereafter. In three patients, the urinary excretion of uric acid transiently but inexplicably increased greatly in the first 48 hr of allopurinol therapy. One patient had an excretion of 2,500 mg during the first 24 hr of allopurinol administration, whereas the daily excretion of uric acid before treatment was less than 1 g. It is, therefore, suggested that fluid intake be increased in the first few days of allopurinol therapy, especially when urolithiasis or hyperexcretion of urate has been documented. The possibility that excessive excretion of the oxypurines—hypoxanthine and xanthine—would lead to formation of calculi has not materialized, probably because of the greater renal clearances and separate solubilities[1] of these oxypurines.

The phenomenon of continuing episodes of gout despite the patient's having normal serum levels of uric acid while under treatment has been known for many years. Since allopurinol possesses no antiinflammatory effect, attacks of gout can recur for many months after treatment has been started. It is now our practice to give colchicine, 0.6 mg twice daily for six months, to each patient who begins a course of allopurinol, and to each patient who still shows tophaceous deposits. In this way, the frequency of posttreatment attacks is greatly reduced. Allopurinol may be used in con-

junction with uricosuric agents in severe tophaceous disease. This combination of agents further decreases serum uric acid content so that tophi will disappear more quickly[1] than if uricosuric agents were used alone. There was no toxicity to renal, hepatic, or hematopoietic function in the patients in our study. One patient continued to take the drug despite a chronic pruritic dermatitis attributed to it.

Current indications for the use of allopurinol are as follows: tophaceous gout, and when uricosuric drugs are ineffective; gout with renal insufficiency; recurrent uric acid calculi; secondary gout; and as prophylaxis against uric acid nephropathy. Since the latter complication is more likely to occur in patients whose initial serum content of uric acid is more than 11 mg per 100 ml, those patients should receive allopurinol to decrease serum uric acid content to normal before and during cytolytic therapy.

SUMMARY

Allopurinol was given to 15 patients with gout, six patients with uric acid calculi, and one with hyperuricemia secondary to lymphosarcoma. When administered along with initial colchicine therapy, allopurinol afforded excellent prophylaxis against gout in all patients. It abolished the incidence of uric acid calculi in six patients with uric acid lithiasis, and prevented uric acid nephropathy in one patient with secondary gout. In one patient with early gouty nephropathy, allopurinol therapy led to a return of normal renal function and urinary sediment. Allopurinol has several advantages over conventional uricosuric drugs whose action may be unreliable under various clinical circumstances. Allopurinol is the most reliable drug to decrease serum uric acid content in patients with gout, and is currently the agent of choice in treating patients who have uric acid lithiasis or secondary hyperuricemia.

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