Allopurinol is known chemically as 1,5-dihydro-4-[3,4-dihydropyridine-2(1H)-yl]-1,
5,10,7,9,6-dihydro-10-0xo-2,6,8(3H)-trione. It is an inhibitor of xanthine oxidase, which is
inhibited by the action of allopurinol and is metabolized to oxipurinol. Allopurinol is metabolized
to oxipurinol, which in turn is metabolized to oxypurines. The metabolism of allopurinol and
oxipurinol is discussed in detail in the metabolic pathways section.

CLINICAL PHARMACOLOGY

Allopurinol is a uricosuric agent, without disrupting the biosynthesis of purines. It
reduces the production of uric acid by inhibiting the biochemical reactions immediately preceding its
formation. Allopurinol is a structural analogue of the natural purine base, hypoxanthine. It is an
inhibitor of xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to
xanthine and of xanthine to uric acid, the end product of purine metabolism in man.

Allopurinol acts on purine catabolism, without disrupting the biosynthesis of purines. It
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such as hypertension and diabetes mellitus, periods laboratory parameters of renal function, particularly BUN and serum creatinine or creatinine clearance, should be performed and the patient's dosage of allopurinol reassessed. The prothrombin time should be reassessed periodically in the patients receiving dicumarol who are given allopurinol.

Drug Interactions
In patients receiving mercaptopurine or IMURAN (azathioprine), the concomitant administration of 300 to 600 mg of allopurinol per day will require a reduction in dose to approximately 50% of the usual dose of mercaptopurine or azathioprine. Subsequent adjustment of doses of mercaptopurine or azathioprine should be made on the basis of therapeutic response and the appearance of toxic effects (see CLINICAL PHARMACOLOGY).

It has been reported that allopurinol prolongs the half-life of the anticoagulant, dicumarol. The clinical basis for this drug interaction has not been established but should be noted when allopurinol is given to patients already on dicumarol therapy.

The reports that the concomitant use of allopurinol and thiazide diuretics may contribute to the enhancement of allopurinol toxicity in some patients have been reviewed in an attempt to establish a cause-and-effect relationship, and a mechanism of causation. Review of these reports indicates that the patients were mainly receiving thiazide diuretics for hypertension and that tests to rule out decreased renal function secondary to hypertension nephropathy were not often performed. In those patients in whom renal insufficiency was documented, however, the recommendation to lower the dose of allopurinol was not followed. Since a cause-and-effect relationship has not been established, current evidence suggests that renal function should be monitored in patients on thiazide diuretics and allopurinol even in the absence of renal failure, and dosage levels should be even more conservatively adjusted in those patients on such combined therapy if renal function is detected. An increase in the frequency of skin rash has been reported among patients receiving ampicillin or amoxicillin concurrently with allopurinol compared to patients who are not receiving such a combination. This association has not been established.

Enhanced bone marrow suppression by cyclophosphamide and other cytotoxic agents has been reported among patients with neoplastic disease, except leukemia, in the presence of allopurinol. The concomitant administration of patients with lymphoma on combination therapy, allopurinol did not increase the marrow toxicity of patients treated with cyclophosphamide, procarbazine, and/or mechlorethamine. Tolbutamide's conversion to inactive metabolites has been inhibited by dialyzed from rat liver. The clinical significance, if any, of these observations is unknown.

Chlorpropamide's plasma half-life may be prolonged by allopurinol, since allopurinol and chlorpropamide are dialyzable to a similar extent in the renal tubule. The risk of hypoglycemia secondary to this mechanism may be increased if allopurinol and chlorpropamide are given concomitantly. Such patients should be monitored closely for signs of hypoglycemia. Rare reports indicate that cyclosporine levels may be increased during concomitant treatment with allopurinol. Further studies of cyclosporine levels and possible adjustment of cyclosporine dose levels should be considered when these drugs are coadministered.

Drug/Laboratory Test Interactions
A great deal is known about the influence of drugs on laboratory test results. Pregnancy

Teratogenic Effects: Pregnancy Category C. Reproductive studies have been performed in rats and rabbits at doses up to twice the usual human dose (5 mg/kg/day), and it was concluded that there was no impaired fertility or harm to the fetus due to allopurinol. There have been published data of a study in pregnant women given 50 to 100 mg/kg allopurinol during the first trimester. In the rabbit, there was no excess fetal resorption, malformations, or other evident effects. In man, the results of available data are insufficient to make an evaluation. While adjusting the dosage of allopurinol in patients who are being treated with colchicine concurrently, it is possible to reduce serum uric acid to normal or, if desired, to as low as 2 to 3 m g/dL and keep it there indefinitely.

Preparations
The dose of allopurinol recommended for management of recurrent calcium oxalate stones in hyperuricosuric patients is 200 to 300 mg/day in divided doses or as a single daily dose. Tolerability has been enhanced by the use of the controlled release formulation. The dose of allopurinol should be adjusted upward if the control of the hyperuricosuria based upon subsequent 24 hour urine urate determinations. Clinical experience has shown that a total daily dose of 300 mg of allopurinol is suitable. When the clinical control of hyperuricosuria is not satisfactory, the maximum daily dose should not exceed 100 mg. With extreme renal impairment (creatinine clearance less than 3 mL/min) the interval between doses can be increased to 48 hours.

The correct size and frequency of dosage for maintaining the serum uric acid just within the normal range is best determined by using the serum uric acid level as an index. As the prevention of uric acid nephropathy is the major objective in gouty arthritis, treatment with 600 to 800 mg daily for three or four days is advisable together with a high fluid intake. Otherwise similar considerations to the above recommendations for treating patients with gout govern the regulation of dosage for maintenance purposes in secondary hyperuricemia.

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