Postchemotherapy Purine Excretion in Lymphoma Patients Receiving Allopurinol

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ABSTRACT

The urinary excretion of hypoxanthine, xanthine, and uric acid was measured prior to and following chemotherapy in 11 patients with rapidly growing chemotherapy-sensitive lymphomas who were receiving concomitant allopurinol therapy. Mean maximal total daily urinary excretions of these purines post-chemotherapy were: uric acid, 807 mg/day; hypoxanthine, 343 mg/day; and xanthine, 638 mg/day. The mean maximal postchemotherapy urinary concentrations of uric acid, hypoxanthine, and xanthine were 288, 115, and 179 mg/liter, respectively. Mean total daily urinary excretion of uric acid, hypoxanthine, and xanthine rose 2.2-, 6.6-, and 6.9-fold, respectively, following initiation of antineoplastic therapy. Although standard doses of allopurinol did not prevent a postchemotherapy increase in the excretion of uric acid or hypoxanthine, the urinary concentrations of both compounds remained below their solubility in urine at pH 7 in all 11 patients studied. However, the urinary concentration of xanthine exceeded its solubility in urine at pH 7 in six of the 11 patients. In three of the six patients whose urinary xanthine concentration exceeded its solubility in urine, transient renal failure developed in association with the increased excretion of xanthine. These studies indicate that, despite the use of conventional doses of allopurinol, the urinary excretion of uric acid may still increase following massive tumor lysis, and urinary excretion of xanthine can increase to concentrations potentially causing xanthine nephropathy.

INTRODUCTION

An association of hyperuricemia with leukemia and lymphoma has been recognized for more than a century (23). The hyperuricemia of malignant disease is due to increased cell turnover with breakdown of nucleic acid purines and subsequent catabolism of these purines to uric acid. Uric acid is sparingly soluble in water, being slightly less soluble at low solvent pH and low ionic strength. Even at normal serum urate levels, concentrations of uric acid in the urine approach the solubility of uric acid in water (15). It is, therefore, not surprising that conditions which lead to overproduction of uric acid and increased urinary uric acid excretion may result in precipitation of uric acid crystals within the collecting ducts and deep cortical and medullary vessels where uric acid concentration and acidification is maximal (7, 20). This precipitation results in a marked decline in renal blood flow and glomerular filtration with the subsequent development of acute renal failure.

Although occasional patients with leukemia and lymphoma developed clinically significant hyperuricemia prior to the mid-1950's, hyperuricemic acute renal failure became a major clinical problem with the development of effective chemotherapeutic regimens for these diseases. Sandberg et al. (24) in 1956 demonstrated a marked increase in uric acid excretion in 13 of 13 patients with acute leukemia following chemotherapy, and Frei et al. (9) in 1963 found a 10% incidence of "severe" uric acid nephropathy following antileukemic therapy for acute lymphocytic leukemia. The development of allopurinol [4-hydroxyprazolo-(3,4-d)pyrimidine] in the early 1960's allowed a method of preventing the complications of hyperuricemia. Allopurinol, through conversion to its metabolite oxipurinol, is a potent inhibitor of the enzyme xanthine oxidase (EC 1.2.3.2) blocking the conversion of hypoxanthine and xanthine to uric acid (Chart 1) (27). In several studies (8, 17) conducted in the mid-1960s, the use of allopurinol (generally in doses of 200 to 800 mg/day) was shown to be effective in decreasing the formation of uric acid and reducing the incidence of uric acid nephropathy in patients with malignant disease. Following publication of these reports, the prophylactic use of allopurinol prior to the initiation of chemotherapy in patients with leukemia and lymphoma has been standard medical therapy.

During the past decade, information regarding the clinical behavior of many neoplastic diseases has increased, and therapy of some of these cancers has improved dramatically. Certain types of lymphomas have been recognized as rather indolent while other lymphoma subtypes have been shown to be rapidly dividing and clinically aggressive (21). Treatment of these rapidly dividing lymphomas [Burkitt's lymphoma, lymphoblastic (T-cell) lymphoma, and diffuse histiocytic lymphoma] has improved dramatically so that a clinical response to chemotherapy is achieved in 80 to 90% of these patients, and rapid tumor lysis is commonly seen (25, 29, 31). In treating patients with chemotherapy-sensitive rapidly growing tumors, we noted that occasionally patients develop transient renal failure after chemotherapy despite the use of allopurinol (11). The potential causes of renal failure in such situations are many but include precipitation of uric acid or other purines in the renal tubules. Uric acid precipitation in the kidney could potentially be avoided by increased doses of allopurinol. However, if xanthine precipitation were the cause of such nephropathy, an increase in the dose of allopurinol would be contraindicated. To determine if increased excretion of end products of purine catabolism could account for unexplained renal failure, we have quantitated the urinary excretion of xanthine, hypoxanthine, and uric acid in a series of patients with rapidly dividing lymphomas. This report presents our findings in 11 patients studied.

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MATERIALS AND METHODS

Subjects. Patients were required to fit the following criteria: (a) histological diagnosis of Burkitt's lymphoma, diffuse histiocytic lymphoma, or lymphoblastic lymphoma (T-cell lymphoma) made by pathologists at either the National Cancer Institute or Vanderbilt University Medical Center using previously described classification schemes (18); (b) widespread disease requiring systemic chemotherapy; (c) no prior treatment with either radiation or chemotherapy; and (d) urine collections prior to and for at least 4 days following initiation of chemotherapy. All patients were treated at the National Cancer Institute, Bethesda, Md.; the Nashville Veterans Administration Medical Center, Nashville, Tenn.; or Vanderbilt University Medical Center, Nashville, Tenn. Informed consent was obtained from all patients. Patients were treated with allopurinol (Zyloprim; Burroughs-Wellcome, Research Triangle Park, N. C.) for 2 to 5 days prior to initiation of chemotherapy and continued on allopurinol for the duration of the study. Doses of allopurinol varied according to the preferences of the physician caring for the patient and ranged from 300 to 600 mg/day. Due to their clinical condition, patients were not placed on a specifically controlled purine diet during the study period. However, total food intake and total purine intake during the study period were generally quite low (purine intake <50 mg/day). Due to their clinical condition, patients were not placed on a specifically controlled purine diet during the study period. Patients were hydrated with a least 3 liters of i.v. fluids per day during and following chemotherapy. Most but not all patients received i.v. sodium bicarbonate to increase urinary pH. Daily 24-hr urine collections were made on all patients prior to and for 4 to 7 days following initiation of chemotherapy. Urinary collections prior to chemotherapy were made at least 24 hr after initiation of allopurinol therapy but prior to initiation of antineoplastic therapy. Urine was collected without preservative and stored at 4° until analysis. At the time of analysis, urine was warmed to 37° and shaken to redissolve any crystals which may have formed by cooling. Urine samples were analyzed for uric acid, xanthine, and hypoxanthine. Patients were treated with chemotherapy regimens thought to be most appropriate for the patient by the attending physician. Although there was no single uniform chemotherapeutic regimen used, all patients were treated aggressively with a combination of at least 3 different antineoplastic agents. The clinical diagnosis and treatment regimens for all patients are listed in Table 1. No patient received a chemotherapeutic regimen containing a purine analog such as 6-thioguanine or 6-mercaptopurine. Methotrexate doses were all less than 20 mg/sq m. All patients were followed closely during the first week postchemotherapy for a clinical response to antineoplastic therapy. A clinical response was defined as a 50% or greater reduction in the size of all measurable tumors without the appearance of any new disease.

Measurement of Uric Acid Concentrations. Urinary uric acid concentrations were measured by the Automatic Clinical Analyzer (DuPont Co., Wilmington, Del.). This assay is based on a kinetic modification of the uricase method which measures the change in absorbance of light at 293 nm which occurs as uric acid is converted to allantoin (3).

Measurement of Xanthine and Hypoxanthine. Urinary concentrations of xanthine and hypoxanthine were determined by high-pressure liquid chromatography or gas chromatography methods described previously (19). These methods involved prepurification of urine samples by either sulfosalicylic acid precipitation or Sephadex G-10 column chromatography according to the method of Sweetman and Nyhan (28). The prepurification removed several potential interfering substances such as nucleotides and nucleosides. Following prepurification, samples were analyzed using either high-pressure liquid chromatography on a C18-Bondapak reverse-phase column (Waters Associates, Inc., Milford, Mass.) using 0.05 M ammonium phosphate buffer (pH 4.5) as the eluent or by gas chromatography on glass columns of 4% SE-30 on 100/120
Supelcoport. Both methods gave a clear separation of xanthine and hypoxanthine from allopurinol, oxipurinol, and uric acid. No interference was noted from caffeine or other methylxanthines using these methods. Sensitivity of these assays was less than 25 ng of xanthine or hypoxanthine for high-pressure liquid chromatography analysis and 200 ng for gas chromatography analysis.

**Measurement of Calcium and Phosphorus Concentrations.** Calcium and phosphorus concentrations were measured by standard spectrophotometric methods performed on an Automatic Clinical Analyzer.

**Measurement of Allopurinol and Oxipurinol Concentrations.** Serum concentrations of allopurinol and its metabolite, oxipurinol, were measured by a previously developed competitive protein binding assay (10). This assay was sensitive to 0.1 μM concentrations of allopurinol or oxipurinol with no significant interference with either xanthine, hypoxanthine, or uric acid.

**RESULTS**

**Clinical Response.** Six patients with diffuse histiocytic lymphoma (Patients 1, 5, 6, 8, 9, and 10), 2 patients with Burkitt's lymphoma (Patients 3 and 7), and 3 patients with lymphoblastic lymphoma (Patients 2, 4, and 11) were studied. A clinical response following chemotherapy was noted in all patients with the exception of Patients 5 and 10 (Table 1). In several patients, the tumor response was dramatic, and a marked reduction in measurable tumor mass was noted within days of treatment (Fig. 1).

**Uric Acid Excretion.** Despite treatment with allopurinol, an increase in the total daily excretion of uric acid was noted in 10 of 11 patients studied following initiation of chemotherapy. A 2.2-fold mean increase in maximal total daily uric acid excretion was found for the entire group of patients following chemotherapy (Table 2). The maximal increase in total daily uric acid excretion in any single patient was a 4-fold rise to a total uric acid excretion of 1.44 g/day. The mean urinary uric acid concentration also increased in 10 of 11 patients post-chemotherapy (Table 2). The mean maximal urinary uric acid concentration post-chemotherapy was 288 mg/liter with a range of 150 to 550 mg/liter. Maximal post-chemotherapy urinary uric acid concentrations exceeded the solubility of uric acid at 37° in urine at pH 5 [150 mg/liter as measured by Klinenberg et al. (15)] in 10 of 12 patients, but in no patient did the urinary concentration of uric acid exceed the solubility of uric acid at pH 7 (2000 mg/liter).

**Hypoxanthine Excretion.** The mean total daily urinary excretion of hypoxanthine following initiation of allopurinol therapy but prior to the administration of chemotherapy was 52 mg/day (Table 2). Following chemotherapy, the maximal total daily urinary hypoxanthine excretion rose 6.6-fold to a mean excretion of 343 mg/day. The maximal excretion of hypoxanthine usually occurred on Days 2 or 3 following initiation of chemotherapy. The greatest increase in hypoxanthine excretion in any single patient following chemotherapy was a 12-fold increase to a total excretion of 898 mg/day. The mean urinary concentration of hypoxanthine also increased post-chemotherapy (Table 2). However, in no patient did the urinary hypoxanthine concentration exceed the solubility of hypoxanthine in urine at either pH 5 (1400 mg/liter) or pH 7 (1500 mg/liter) (15).

**Xanthine Excretion.** The daily pre-chemotherapy and maximal daily post-chemotherapy excretion of xanthine for each of the patients studied is shown in Table 3. Following chemotherapy, the mean daily urinary xanthine excretion rose 6.9-fold. The maximal daily urinary xanthine excretion for any single patient was seen in Patient 2 who had a 23-fold increase to a maximal daily xanthine excretion of 1.88 g/day following chemotherapy.
chemotherapy. The urinary xanthine concentration prior to the initiation of chemotherapy and the maximal urinary xanthine concentration postchemotherapy for each patient studied is also shown in Table 3. In 6 of the 11 patients studied (Patients 2, 4, 6, 7, 8, and 11), the urinary xanthine concentration exceeded the solubility of xanthine in urine at both pH 5 (50 mg/liter) and at pH 7 (150 mg/liter) (15).

Crystals were noted in the sediment of all patients studied postchemotherapy. No renal stones were passed in any patient. Although several types of crystals were seen in many patients, all patients except Patients 3, 5, and 10 demonstrated the type of crystals shown in Fig. 2, which were nonspecific but similar in morphology to xanthine crystals. In Patients 8–12, urine samples postchemotherapy were centrifuged, and the urinary sediment was dissolved in 0.05 M ammonium phosphate buffer and analyzed by high-pressure liquid chromatography. Absorbance peaks corresponding to xanthine made up 60, 50, 16, and 72% of the total absorbance of the urinary sediment in these patients. Thus, by morphology and chromatography analysis, significant xanthine crystaluria was present in many patients.

Clinical Course Postchemotherapy. Of the 11 patients studied, renal failure (serum creatinine, >1.4 mg/dl) was noted in 4 patients (Patients 2, 7, 9, and 11) postchemotherapy. Serum oxipurinol concentrations in these 4 patients were 40, 70, 38, and 36 µM. These values were not significantly different from oxipurinol concentrations in patients not developing renal failure [41 ± 14 (S.D.) µM] and were within what is considered to be the normal range of therapeutic serum oxipurinol concentrations (12). No definite correlation could be made between serum oxipurinol or serum uric acid levels and the development of renal failure. One of these 4 patients (Patient 9) had an abnormal serum creatinine (1.4 mg/dl) prior to chemotherapy. This patient had radiological evidence of partial ureteral obstruction secondary to enlarged lymph nodes prior to initiation of chemotherapy. On the day following chemotherapy, the serum creatinine in this patient rose to 1.6 mg/dl and then returned to normal by the third day following chemotherapy. The elevated serum creatinine in this patient was felt to be partially due to ureteral obstruction and not solely due to tumor lysis. In Patients 2, 7, and 11, serum creatinine values were normal (<1.4 mg/dl) prior to initiation of chemotherapy. Serum creatinine values in these 3 patients rose to 2.0, 2.8, and 2.7 mg/dl, respectively, postchemotherapy and then returned to normal by Day 5 following chemotherapy. There was no evidence of urinary tract obstruction in any of these 3 patients. No known nephrotoxic drugs such as aminoglycoside antibiotics were administered to these patients during this study period. The low doses of methotrexate (10 mg/sq m) given Patients 7 and 11 are not usually associated with renal toxicity.

Renal failure in Patients 2, 7, and 11 was felt to be secondary to tumor lysis. Laboratory evaluations in these 3 patients pre- and postchemotherapy are shown in Table 4. Maximal postchemotherapy uric acid concentrations were 160, 130, and 310 mg/liter, respectively. Creatinine clearance measurements fell to 28, 12, and 19 ml/min posttreatment. The maximal rise in serum creatinine occurred on Days 2 and 3 postchemotherapy and coincided with the maximal rise in urinary xanthine excretion as shown in Chart 2. Mean urine volumes for the 4 days following chemotherapy were 7400 ml/day in Patient 2, 3100 ml/day in Patient 7, and 3200 ml/day in Patient 11. Clinical tumor lysis in all of these 3 patients (2 patients with lymphoblastic lymphoma and one with Burkitt’s lymphoma) was rapid with nearly complete disappearance of massive disease within 1 week of therapy (Fig. 1). These 3 patients also had the

### Table 3

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Mean: 93 638<br>
6 9-fold increase.

### Table 4

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Chart 2. Serum creatinine and urinary xanthine concentrations in patients developing renal failure postchemotherapy. Serum creatinine concentrations (A) and urinary xanthine concentrations (B) for the 3 patients developing renal failure are plotted against time in days with Day 0 being the day chemotherapy was initiated. All patients were receiving allopurinol during the study period. , values for Patient 2; , values for Patient 7; , values for Patient 11.
highest postchemotherapy urinary xanthine concentrations of any patients studied.

DISCUSSION

Doses of 200 to 800 mg of allopurinol per day are generally effective in preventing hyperuricemia following treatment of most malignant disease (8, 17). However, with certain types of neoplasms, chemotherapy is exceptionally effective, and rapid tumor lysis is commonly seen. In such situations, a massive release of nucleic acid purines could be expected with the potential for precipitation of such purines in the renal tubules. The development of renal failure in patients undergoing treatment for rapidly growing chemotherapy-sensitive tumors is not uncommon. Cohen et al. (6) have recently reported a 38% incidence of azotemia in patients undergoing therapy for Burkitt’s lymphoma. Standard doses of 300 to 400 mg of allopurinol per day have been used in these patients to prevent hyperuricemia, but investigations have not been carried out to determine if such doses are appropriate.

Normal urinary excretion of uric acid in humans is under 800 mg/day while that of either hypoxanthine or xanthine is less than 30 mg/day (14, 26). Following administration of allopurinol to patients with primary gout, the renal excretion of uric acid falls while total oxipurine (hypoxanthine plus xanthine) excretion increases to 40 to 200 mg/day with 55 to 70% of that total being xanthine (22, 30). In most cases of primary gout, the increase in total oxipurine excretion is less than the decrease in uric acid excretion. This deficit in total urinary excretion is a result of feedback inhibition of de novo purine biosynthesis occurring as a result of allopurinol therapy (5). In patients who develop hyperuricemia as a result of rapid tumor lysis, release of preformed purines results in the increased formation of uric acid while the contribution of de novo purine synthesis plays a less significant role in the pathogenesis of hyperuricemia in this situation. The major mechanism of action of allopurinol in these patients is as a xanthine oxidase inhibitor, and an increase in oxipurine excretion would be expected to more closely parallel the fall in uric acid excretion. As a result, clinically significant hyperxanthinuria would be more likely to develop following rapid tumor lysis as compared with primary gout. Indeed, most of the reported cases of xanthine nephropathy secondary to allopurinol use have been described in association with rapid tumor lysis (1, 2, 11).

In our present study, an overall increase in total purine excretion occurred postchemotherapy. This is in contrast to the findings of some previous reports of allopurinol use in patients with malignant disease (17) and is probably the result of selection of a group of patients with rapidly dividing tumors and the improvement in treatment for these tumors over the past decade. Allopurinol therapy was effective in preventing major increases in uric acid excretion in our patient population. However, with the massive tumor lysis generally seen in this group of lymphoma patients, a 2.2-fold increase in uric acid excretion was noted following chemotherapy despite allopurinol use. This increase was great enough to exceed the solubility of uric acid in urine at pH 5 in 10 of 12 patients, but in no patients did it exceed solubility of uric acid in urine at pH 7. The excretion of hypoxanthine increased 6.6-fold in our patient population postchemotherapy. However, because of its greater solubility in urine compared to uric acid or xanthine, clinical nephropathy secondary to hypoxanthine precipitation is unlikely to occur.

An overall 6.9-fold increase in urinary xanthine excretion was noted in our patients following chemotherapy. Xanthine is less soluble in urine than is uric acid [50 versus 150 mg/liter at pH 5 and 130 versus 2000 mg/liter at pH 7 (15)]. Urinary xanthine concentrations exceeded the solubility of xanthine in urine at pH 7 in 6 of 11 patients studied. In 3 of these 6 patients, a transient rise in serum creatinine and a fall in creatinine clearance were noted postchemotherapy. However, factors other than pH, such as ionic strength, salt concentration, solubilizing factors, and the presence of other urinary constituents, are important determinants of crystal formation (7). The influence of such factors may explain the lack of renal impairment in some patients with urinary concentrations of xanthine greater than 150 mg/liter. All 3 patients who developed renal failure in our series had dramatic clinical responses to treatment and had the highest urinary concentrations of xanthine postchemotherapy. The increase in urinary xanthine excretion correlated directly with the rise in serum creatinine seen in these patients. Although other potential causes of renal failure such as transient hypotension, urate nephropathy, or calcium phosphate nephropathy cannot be excluded, we believe on the basis of the magnitude of xanthine excretion, its limited solubility in urine, and the appearance of urinary crystals that xanthine nephropathy is one important potential cause of transient renal failure seen in these 3 patients. Direct proof of this etiology would require chemical identification of precipitated material in the renal tubules.

Renal failure noted in this patient population was generally mild and transient, but severe life-threatening renal failure secondary to xanthine nephropathy has occurred (1, 11). Even mild transient renal failure may aggravate concomitant metabolic abnormalities such as lactic acidosis or hyperphosphatemia which can occur in these patients (4, 6). In addition, several antineoplastic agents such as methotrexate and bleomycin are excreted through the kidney, and renal failure may lead to delayed drug excretion and increased toxicity. To prevent these complications, the potential for xanthine nephropathy should be minimized, if possible.

Therapy to avoid purine precipitation in this clinical situation may be difficult. Increased xanthine production would be avoided if allopurinol were eliminated, but all purines would then be converted to uric acid and uric acid nephropathy would probably be universal. The use of allopurinol divides the total purine load between uric acid, xanthine, and hypoxanthine (Chart 1). Since the solubility of each of these purines is independent of the others, a greater total purine load can be excreted in the kidney without purine precipitation. Lower doses of allopurinol could potentially allow for more xanthine to be converted to uric acid. However, even with the normal levels of oxipurinol found in our patients, mild increases in uric acid excretion were noted postchemotherapy. We therefore recommend that patients receive 300 to 600 mg of allopurinol per day prior to chemotherapy and that vigorous hydration be used to decrease the concentration of excreted purines.

A more gradual breakdown of tumor mass would help to minimize the potential for nephropathy as less purine would be presented to the kidney. Lower doses of antineoplastic drugs may allow for more gradual tumor lysis but may also compro-
miser the chance for achieving a complete remission. Since presently available treatment regimens have the potential for cure in these lymphomas (25, 29, 31), it is difficult to recommend altering doses of drug which may decrease the chance of clinical remission.

Urinary alkalinization has usually been recommended as a method for preventing uric acid nephropathy. However, the pK_a of uric acid is at 5.6 while that of xanthine is at 7.4. Although urinary alkalinization may help to prevent uric acid nephropathy, urinary alkalinization may be of little benefit in preventing xanthine nephropathy as the urinary pH needs to be raised to 7.5 to significantly increase the solubility of xanthine. Attaining a urinary pH of over 7.5 may be also associated with significant systemic alkalisation. Even if such a urinary pH is achieved, it may have a minor effect in preventing nephropathy. Conger and Falk (7) have suggested that high tubular flow is the primary mechanism of protection in acute urate nephropathy and that urinary alkalinization plays a minor preventive role. The major therapeutic factor in preventing purine nephropathy is the institution of good hydration (4 to 5 liters/day, if possible) prior to and for 4 to 5 days following chemotherapy. If significant renal failure develops despite adequate hydration, hemodialysis should be instituted. Hemodialysis has been shown to be effective in the treatment of hyperuricemic renal failure and should work as well for hyperxanthinuric renal failure (16).

Our studies suggest that commonly used doses of allopurinol prevent significant increases in uric acid excretion even in patients undergoing rapid tumor lysis. However, hyperxanthinuria is a common finding in these patients, and this hyperxanthinuria may potentially lead to renal failure. Hydration and administration of doses of 300 to 600 mg of allopurinol per day should be given to such patients. Even with such treatment, purine nephropathy may occasionally occur following massive tumor lysis.

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REFERENCES

Fig. 1. Chest roentgenograms of Patient 2 before chemotherapy and 2 and 7 days postchemotherapy showing rapid reduction in size of the mediastinal mass with time.

Fig. 2. A, crystals found in the urinary sediment of Patient 8; B, urinary sediment formed by the addition of xanthine to normal urine. × 320.
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