Hyperuricemic Nephropathy: A Complication of Acute Leukemia in Children

JAMES C. M. CHAN, M.D.

Professor and Director, Nephrology Section, Department of Pediatrics, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

Introduction

In order to provide a point of reference for a rational approach to the therapy of acute uricemic nephropathy, the metabolic pathways leading to the production of uric acid will be briefly reviewed.

Uric acid is the end-product of adenine and guanine metabolism. Relevant to this discussion is the xanthine oxidase enzyme which catalyzes the conversion of hypoxanthine to xanthine and xanthine to uric acid. In children with acute leukemia the increasing production and subsequent destruction of white blood cells result in the rapid elevation of uric acid concentration in the plasma, especially during treatment with antineoplastic drugs. This in turn may lead to the development of acute hyperuricemic nephropathy.1–4

The uric acid deposition in the renal medulla causes obstructive uropathies. This occurrence is not uncommon in children treated for reticuloendothelial malignancies, sarcoma and acute lymphocytic leukemia.

Incidence

The work done at the National Cancer Institute of the National Institutes of Health (NIH) showed that 6 out of 57 patients with acute leukemia developed uric acid nephropathy.4 The treatment had consisted of methotrexate, 6-mercaptopurine, hydrocortisone and cortisone. The duration of treatment before the clinical onset of hyperuricemic nephropathy was from three to six days. The maximum elevation of white cells was 11,800 to 18,000 per mm$^3$; of uric acid from 17 to 71; and of BUN from 51 to 212 mg/100ml.

A number of subsequent reports have amply confirmed and extended these observations of Frei et al.4 and a number of conclusions can be made.

Risk Factors

Uric acid nephropathy is more prone to develop in the treatment of acute lymphocytic leukemia when the following conditions are present: elevation of white blood cells to more than 20,000/mm$^3$, marked adenopathy, especially in the mediastinum, and massive hepatosplenomegaly.

The histology of severe uric acid nephropathy includes intratubular hydronephrosis and infarction from uric acid obstruction5,6; the milder and more common form of uric acid nephropathy shows marked renal enlargement produced by the intense interstitial leukemic infiltration; the glomeruli and tubules are intact. There is a good correlation between the kidney
and liver size in patients with less than 5% leukemic infiltration of these organs.  

Treatment  
The first two modes of treatment rely on the provisions of a more favorable situation for the deposition of uric acid which is reduced when the urinary pH is made alkaline in excess of 6, beyond which point the solubility of uric acid is increased in an exponential fashion.

To insure a good urine output, intravenous 5% dextrose/water is administered at a rate of 3000 ml/m²/day. To promote uric acid solubility and therefore enhance excretion, the urine may be made alkaline by administering intravenous sodium bicarbonate at a dosage calculated to elevate the serum bicarbonate by 10 mEq/liter, and/or the use of a carbonic anhydrase inhibitor acetazolamide to block the renal tubular reabsorption of bicarbonate. The aims of these general measures are to achieve a urinary pH in excess of 6 and a urine volume in excess of 60 ml/m²/hour.

If the urine output is less than 60 ml/m²/hour after rehydration, mannitol (25% aqueous solution) is given initially over a 5- to 10-minute period in a test dose of 6.25 gm in children weighing less than 30 kg and 12.5 gm in children weighing over 30 kg. If diuresis ensues, additional mannitol is administered in the same dose every 6 hours to achieve a urine output of at least 60 ml/m²/hour.

It is important to obtain and record urine volume, pH, body weight, vital signs, blood uric acid, electrolytes, BUN, and calcium concentrations every 12 to 24 hours.

Normal glomerular filtration rates are achieved within 2 to 14 days of treatment of hyperuricemia with fluids, bicarbonate and acetazolamide.

Special Therapy  
The rapid removal of uric acid can be achieved by either peritoneal dialysis or hemodialysis.

Peritoneal dialysis removes uric acid at a rate of 15 ml/min, but hemodialysis is at least five times more effective. The decision on when to institute these procedures is a clinical one and is based on the physician's past experience and the patient’s status. One example of this complex clinical decision is shown in the Figure.

Allopurinol  
Allopurinol (10 mg/kg/day initial oral dose) is a useful drug for the treatment of hyperuricemia. Allopurinol is a potent inhibitor of xanthine oxidase for which it is also a substrate.

Although the incidence of side effects is very low, the potential complications of allopurinol treatment should always be kept in mind. These include skin and blood dyscrasias, malaise, fever, complaints of nausea, headache, vomiting, vertigo, drowsiness and gastric irritation, muscle ache, elevation of SGOT/SGPT, leucocytosis, leucopenia and, rarely, peripheral neuritis and bone marrow depression.

Acute uric acid nephropathy occurred at the time of leukemic relapse. Diuresis did not occur despite all the general treatment procedures. Peritoneal dialysis was only partially successful in the removal of 4 gm of uric acid in 24 hours without lowering the serum uric acid concentration. Hemodialysis was instituted and removed over 17 gm of uric acid resulting in a decrease of serum uric acid from 87 to 29 mg/dl. Immediately following dialysis, he was given 25 gm of intravenous mannitol and was started on allopurinol. However, anuria persisted and a second course of hemodialysis was performed for 6 hours, resulting in a decrease of serum uric acid from 46 to 19 mg/dl. Just before the completion of the dialysis, he voided 340 ml of urine and the output remained adequate thereafter aided by good fluid and conservative medical management.

Figure—Acute uric acid nephropathy and treatment with hemodialysis is illustrated in the clinical course of a 14-year-old white boy.
The use of hemodialysis is dependent on machine availability and the existence of a specially trained nephrology team consisting of dialysis technicians, nurses, surgeons, and nephrologists. Peritoneal dialysis requires less technical hardware and can be initiated more promptly by the nephrologist; whereas, before hemodialysis can be initiated, vascular access and somewhat extensive preparations are needed, especially in small children in the 2- to 3-year age group, where uric acid nephropathy more commonly occurs.

There is a relationship between the days of oliguria before dialysis has been started and the number of days until diuresis begins which has been taken as an indication for the early institution of either of these special procedures within a day or two of anuria and/or rapidly rising serum uric acid concentrations.

Summary

Hyperuricemic acute nephropathy occurs in 10% of patients with leukemia; the intrarenal uric acid deposition results in obstructive uropathy.

The clinical findings which point to the likelihood of renal damage are: first, an initial white blood cell count in excess of 20,000/mm³; second, marked adenopathy especially in the mediastinum; and third, the presence of massive hepatosplenomegaly. The aim of general treatment with fluids and renal alkalization is to promote uric acid solubility and output by maintaining urine pH in excess of 6 and urine volume in excess of 60 ml/m²/hr. The discovery and clinical use of allopurinol, an analogue of hypoxanthine and an inhibitor as well as a substrate of the enzyme xanthine oxidase, is central to the control of hyperuricemia. Allopurinol, as well as its metabolic end-product, alloxanthine, acts at the terminal steps of uric acid metabolism to reduce the production of uric acid and in conjunction with the other general medical therapy, contributes to the reversal of the hyperuricemia.

Finally, the special extrarenal procedures of peritoneal dialysis and hemodialysis can rapidly, efficiently and safely remove the uric acid from the body. The sooner one initiates either of these procedures, the earlier diuresis begins.

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REFERENCES