Efficacy of urate oxidase (uricozyme) in tumour lysis induced urate nephropathy

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Summary  
Urate oxidase (uricozyme) is an enzyme of non-human origin capable of oxidizing human uric acid to allantoin, a highly soluble product at renal tubule pH. We report its efficacy in three patients with acute urate nephropathy due to tumour lysis in chronic lymphatic leukaemia and high grade lymphoma. Two patients had an additional obstructive nephropathy due to ureteric urate crystals. An intravenous infusion (100 units/kg in 50 ml saline over 30 min) was given for between two and five consecutive days. All patients showed a rapid fall in serum urate levels with associated diuresis, correction of metabolic disturbance and full resolution of uraemia within a week. The treatment was well tolerated and caused a rapid resolution of clinical symptoms in all cases. We review the literature relating to the use of this agent both in the treatment of hyperuricaemic acute renal failure and gouty arthritis.

Keywords  
Urate oxidase, urate nephropathy, hyperuricaemia, tumour lysis syndrome

Introduction  
Hyperuricaemia is a well recognized complication of malignant haematological disorders reflecting an increased rate of purine metabolism due to rapid cell turnover. It may be a feature at presentation but more commonly develops following cytolytic therapy due to accelerated purine breakdown. Together with hypocalcaemia, hyperphosphataemia and hyperkalaemia, this complication is an important component of treatment related tumour lysis syndrome (Cohen et al. 1980). Gouty arthritis, although well described, is not a common clinical finding in this setting. Urate nephropathy, due to the precipitation of non-ionized urate at the acid pH of renal tubules and collecting ducts, is a more serious complication. Oliguria is common and the impaired renal function leads to a further accumulation of urate such that some patients require renal dialysis. The associated metabolic disturbance, particularly hyperkalaemia, may lead to early death from cardiotoxicity in a patient with a potentially curable disease (Arsenau et al. 1975; Cohen et al. 1980).

Prophylactic therapy for urate nephropathy consists of intravenous fluids, alkalinization of urine and oral allopurinol before cytotoxic therapy. Established renal failure due to hyperuricaemia may, however, be a presenting feature in patients with highly malignant disease (Post 1961). Allopurinol, a xanthine oxidase inhibitor which prevents the formation of urate from xanthine, has little effect in this situation. In addition, allopurinol may be contraindicated in patients with a previous allergy or who are at risk of major drug interactions, e.g. azathioprine, mercaptopurine therapy. Even if commenced early, allopurinol prophylaxis may not allow full renal protection as xanthine precipitation has been reported to cause renal tubular obstruction (Band et al. 1970).

Urate oxidase is an enzyme responsible for the oxidation of urate to allantoin, a compound which is 10 times more soluble at renal tubule pH and therefore more readily excreted. Man and the great apes differ from other mammals in that they lack this enzyme. A urate oxidase of fungal origin (Aspergillus flavus) was first isolated in pure form in 1968 (LaTourneur & Langlois 1968). The enzyme can now be prepared on industrial scale and in a highly purified form. Urate oxidase (uricozyme) is currently marketed as standard urolytic therapy in France and Italy and is available on a named patient basis in the UK. A recombinant urate oxidase produced by a genetically modified Saccharomyces cervisiae strain is being developed.

We report the efficacy of intravenous urate oxidase in three patients for the treatment of tumour lysis induced urate nephropathy in malignant haematological disease.
Case reports

Case 1

A 72-year-old woman with Stage C chronic lymphatic leukaemia and increasing white cell count and organomegaly was commenced on fludarabine therapy after becoming refractory to previous treatment. The patient was intolerant of allopurinol having developed a generalized skin rash with previous exposure. Fludarabine, 25 mg/m², was administered as a daily intravenous infusion for 5 days. Her full blood count (FBC) at the start of therapy was Hb 11.3 g/dl, WBC $105 \times 10^9$/l (lymphocytes $100 \times 10^9$/l), platelets $82 \times 10^9$/l. Serum urea, creatinine and electrolytes were all normal.

The patient presented 3 days after completion of therapy with loin pain, nausea and vomiting. She was clinically dehydrated and oliguric with biochemical features of tumour lysis syndrome (sodium 136 mmol/l, potassium 7.0 mmol/l, bicarbonate 14 mmol/l, urea 42.9 mmol/l, creatinine 416 µmol/l, calcium 1.76 mmol/l, phosphate 4.48 mmol/l and urate 1780 µmol/l (N.R. 180–320)). Her FBC showed a rapid fall in the white cell count with Hb 9.9 g/dl, WBC $4.2 \times 10^9$/l, platelets $55 \times 10^9$/l, consistent with massive cell lysis. Supportive therapy with fluids, bicarbonate, dextrose, insulin and oral calcium resonium was given but serum creatinine and urate remained markedly elevated at 424 µmol/l and 1761 µmol/l, respectively.

Urate oxidase was started at a dose of 100 units/kg daily by i.v. infusion in 50 mls NaCl 0.9% over 30 min on five consecutive days. By the second day of treatment the serum urate had fallen to 29 µmol/l and a diuresis was established, whilst by day 8 all biochemical disturbance was corrected (serum creatinine 92 µmol/l) and the patient much improved clinically (Figure 1).

Figure 1. Changes in serum urate and creatinine following urate oxidase therapy (Case 1). ●, Urate (µmol/l). ○, Creatinine (µmol/l).

Three months post therapy the patient remains well and renal function is maintained with creatinine 98 µmol/l and serum urate 270 µmol/l. Allopurinol was subsequently recommenced without adverse reaction.

Case 2

A 55-year-old man presented with a short history of lethargy, night sweats and cervical lymphadenopathy. His FBC was Hb 12.7 g/dl, WBC $21.0 \times 10^9$/l (lymphocytes $100 \times 10^9$/l) and platelets $23 \times 10^9$/l. Large pleomorphic nucleolated lymphoid cells with basophilic cytoplasm were seen on the blood film. Immunophenotyping identified a neoplastic population of cytoplasmic IgG kappa restricted cells, positive for CD19, CD23, FMC7 and HLA-DR and CD10 (weak). The bone marrow trephine biopsy contained a diffuse lymphoid infiltrate, marked apoptosis and grade 3 reticulin fibrosis. Cytogenetic analysis on peripheral blood revealed multiple complex abnormalities, including t(14:18) (q32:q21).

The patient developed severe bilateral colicky loin pain, a deteriorating urine output and rising serum creatinine. An intravenous urogram identified normal sized kidneys, but with poor and delayed excretion together with bilateral hydronephrosis. The level of obstruction was not apparent but at cystoscopy a urate sludge was noted to be occluding both ureteric orifices. The ureters were probed with guide wires and bilateral stents were inserted with issue of urine.

In the 24 h after this procedure urine output improved but was inconsistent and inappropriately low (total 1560 ml) with a creatinine of 455 µmol/l. A five day course of urate oxidase, 100 µg/kg, was started the following day. A rapid fall in serum urate was noted. (91 µmol/l on day 2, 28 µmol/l on day 4 of treatment) together with a fall in serum creatinine (157 µmol/l on day 5) and prompt diuresis (total 4300–6000 ml/day). All abdominal and loin pain cleared.

Allopurinol therapy was commenced prior to induction chemotherapy and serum urate remained normal with no further renal complications. After an initial response to therapy the patient died 3 months later of a neutropenia related septicaemia.

Case 3

A 72-year-old lady with Stage C chronic lymphatic leukaemia, was initially commenced on intravenous flu-
fludarabine therapy in May 1996 after becoming refractory to oral agents. Five courses of fludarabine 25 mg/m² were given monthly with allopurinol cover. The treatment was effective in normalizing her white cell count and clearing cervical lymphadenopathy but extensive para-aortic disease remained.

In July 1997 fludarabine was restarted because of an increasing white cell count (Hb 14.7 g/dl, WBC 104 × 10⁹/l, lymphocytes 95.6 × 10⁹/l), platelets 167 × 10⁹/l) and lymphadenopathy. A second course was given 1 month later when allopurinol had inadvertently been discontinued. Serum creatinine prior to therapy was recorded. White cell count was 44.8 (lymphocytes 40.7) × 10⁹/l, (lymphocytes 95.6 × 10⁹/l), increasing white cell count (Hb 14.7 g/dl, WBC 104 × 10⁹/l), K⁺ 7.6 mmol/l, bicarbonate 17 mmol/l, calcium 2.24 mmol/l, phosphate 3.27 mmol/l, magnesium 1.4 mmol/l and urate 1385 μmol/l. Her urine output was maintained but remained suboptimal (1270 ml/24 h) despite hyperhydration and supportive therapy with bicarbonate, calcium resonium, dextrose and insulin. Abdominal ultrasound showed extensive para-aortic lymphadenopathy (nodes up to 5 cm as before) with mild bilateral hydronephrosis and multiple small stones in the renal pelves. Urate nephropathy was diagnosed and urate oxidase was given on two consecutive days (dose as before) following which a diuresis was noted (output 5190 ml/24 h) with a fall in serum creatinine to 295 (peak 371) μmol/l and urate to 22 μmol/l. Allopurinol was then recommenced. Despite the marked clinical and biochemical improvement she was investigated with respect to ureteric compression from the central abdominal nodes. At cystoscopy, on day 4, urate crystals were observed issuing from the left ureteric orifice. No definite features of external compression were seen on retrograde pyelograms but bilateral stents were inserted as a prophylactic measure. Over the following days the diuresis continued with full resolution of acidosis, hyperkalaemia and clinical symptoms. By day 8 serum creatinine had fallen to 115 μmol/l and urate was controlled at 101 μmol/l. One month later the patient has not required further therapy and continues on allopurinol with a normal serum creatinine and urate.

Discussion

Three patients are described with hyperuricaemic acute renal failure associated with tumour lysis syndrome. Two patients developed tumour lysis following fludarabine therapy for advanced CLL, this now being a recognized complication in patients refractory to first line therapies (List et al. 1990). A third patient with a high grade non-Hodgkin’s lymphoma developed urate nephropathy prior to induction chemotherapy. All three were treated with intravenous urate oxidase which induced precipitous falls in serum urate, followed by a prompt diuresis with associated correction of biochemical disturbances and fall in serum creatinine. All symptoms relating to uraemia, acidosis and ureteric obstruction promptly settled.

Despite all patients being given full supportive therapy and hyperhydration, a diuresis was only documented following treatment with urate oxidase. Ureteric stenting was performed in two patients with additional obstructive nephropathy due to urate crystals. Patient 2, however, was still oliguric post stenting and only improved with uricolyis, while patient 3 underwent a diuresis post uricolyis and prior to prophylactic stenting. Uricolyis with hyperhydration and alkalization of urine were therefore thought to be the most important aspects of management. Urate oxidase was simple to administer and no adverse reactions were encountered.

Urate oxidase has been extensively used in France and Italy but remains virtually unknown in the United Kingdom. It has been used both in the prophylaxis (Vigo et al. 1981; Robert et al. 1976; Masera et al. 1982) and treatment (Kissel et al. 1975; Robert et al. 1976; Jankovic et al. 1985) of urate nephropathy in paediatric and adult patients with malignant haematological disease. It is particularly of value in patients with high grade lymphoma/acute leukaemias with bulky lymphadenopathy, hyperleucocytosis and exquisite chemosensitivity. Urate oxidase is also effective in the treatment of hyperuricaemia and gouty arthritis post cardiac transplant when allopurinol is contraindicated due to concomitant azathioprine therapy (Ippoliti et al. 1990; Rozenberg et al. 1993; Rozenberg et al. 1995).

Urate oxidase has few side-effects. Mild inflammatory reactions at the infusion site have been noted (Kissel et al. 1975) while allergic reactions, with rash or bronchospasm and anaphylaxis, are rare (Vigo et al. 1981). Such reactions appear more likely in allergic individuals or those previously sensitized to Aspergillus antigen. Urate oxidase therapy has been repeated without loss of efficacy (Kissel et al. 1975; Davis et al. 1981), though some patients may develop neutralizing antibodies. Covalent linking of the enzyme to polyethylene glycol (PEG-uricase) may prevent such immunization and prolong in vivo activity (Davis et al. 1981; Chua et al. 1988) A single case of haemolytic anaemia due to glucose-6-phosphate dehydrogenase deficiency following urate oxidase therapy has been reported (Ducros et al. 1991).
Urate oxidase, therefore, appears a safe and effective therapy for urate nephropathy induced by malignant haematological disease and its treatment. It is of particular value in patients intolerant of allopurinol or presenting with established hyperuricaemic acute renal failure. Early use of the drug may circumvent the need for renal support and help to rapidly correct life threatening hyperkalaemia. Recombinant and immunologically modified urate oxidase will soon become available leading to further improvement in the safety profile. A trial of urate oxidase in the prevention of urate nephropathy following induction therapy for high grade haematological malignancies in adults is soon to be initiated in the UK. The results of this study are awaited with interest.

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References


