

Urate oxidase (rasburicase) for treatment of severe acute gout: a case report

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ABSTRACT

A 73-year-old female patient was referred to our department because of gouty arthritis in the right first toe. The patient suffered from progressive renal failure because of pauci-immune necrotising glomerulonephritis. As severe hyperuricaemia would further worsen progredient renal insufficiency and therapy with allopurinol was contraindicated because of renal insufficiency and previous pancytopenia, the patient was treated twice with intravenous rasburicase. This therapy was well tolerated by the patient and led to the decrease of serum uric acid below the detection limit within 24 hours.

Introduction

Gout is a clinical disorder caused by hyperuricaemia, which can lead to an accumulation of urate crystals in joints, soft tissue and kidneys resulting in acute inflammation and pain in joints as well as soft tissues. In the kidney the urate crystals may cause nephrolithiasis and renal insufficiency. For the treatment of acute gout attacks glucocorticoids and nonsteroidal antirheumatic drugs are used, however long-term therapy of chronic gout deserves uricosuric and/or uricostatic drugs for a sustained lowering of serum urate (<6mg/dl) (1). Allopurinol, a hypoxanthine analogue, reduces the urate production by inhibition of the enzyme xanthine-oxidase. This results in the accumulation of the preliminary stages of urate, hypoxanthine and xanthine, which may lead to xanthine nephropathy (2-3).

The endogenous enzyme urate oxidase catalyzes the conversion of the relatively insoluble urate to the water-soluble allantoin easily excreted by the kidney (Fig. 1) (4). This enzyme is still expressed in most mammals, but not in humans anymore (5-6). Rasburicase, as a recombinant urate oxidase, is effectively used for the treatment of hyperuricaemia and prevention of acute renal failure in cancer patients with tumour lysis syndrome.

In the following case acute gouty arthritis with marked hyperuricaemia and progredient renal insufficiency was successfully treated with rasburicase.

Case report

We report the case of a 73-year-old female patient suffering from progressive renal failure and an acute gout attack successfully treated with rasburicase.

The patient was diagnosed in 2001 with pauci-immune necrotising glomerulonephritis. Since then she was treated with azathioprine 50 mg daily leading to sustained remission of the disease. Hyperuricaemia was present since January 2005 and was initially treated with allopurinol (300-600 mg daily). In December 2005 the patient developed pancytopenia with 1.61 T/l erythrocytes (normal 3.8-5.2 T/l), hemoglobin 5 mg/dl (normal 12-16 mg/dl), 2.6 G/l leukocytes (normal: 4-10 G/l) and 45 G/l thrombocytes (normal: 150-350 G/l). As drug-induced pancytopenia was the most likely cause, the combination of azathioprine and allopurinol was withdrawn. Two months later the patient was admitted to our hospital for the first time because of arthritis of the right first toe. The laboratory tests showed raised serum levels of uric acid with 19.1 mg/dl (normal 2.6-6.0 mg/dl), 2.5 mg/dl creatinine (normal 0.6-1.1 mg/dl), 166 mg/dl urea (normal 10-50 mg/dl) and 5.9 mg/dl C-reactive protein (normal 0-0.5 mg/dl) without proteinuria or erythrocyturia. The clinical manifestation as well as laboratory findings led to the diagnosis of an acute gouty attack. As severe hyperuricaemia would further worsen progredient renal insufficiency and therapy with allopurinol was contraindicated because of renal insufficiency and previous pancytopenia, the patient was treated with intravenous rasburicase at a dose of 0.1 mg/kg body weight (Fasturtec™, Sanofi-Aventis). Within 24 hours after administration the serum uric acid level decreased below the detection limit of <0.1 mg/dl, the serum creatinine level to 1.7 mg/dl and the C-reactive-protein level to 2.4 mg/dl. Symptomatically the patient was treated with prednisone at a dose of 10 mg per day leading to rapid disappearance of symptoms of gouty arthritis. Only one month later arthritis recurred and serum uric acid level was elevated again to 9.1 mg/dl. Besides, serum creatinine and erythrocyte sedimentation

Competing interests: none declared.

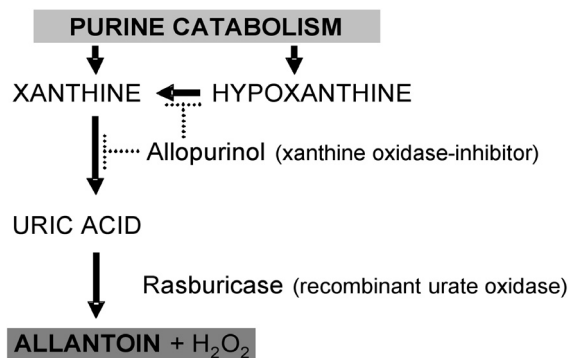


Fig. 1. Purine pathway. Allopurinol reduces the urate production by inhibition of the enzyme xanthine-oxidase. Urate oxidase (rasburicase) catalyzes the conversion of the relatively insoluble urate to the water-soluble allantoin easily excreted by the kidney.

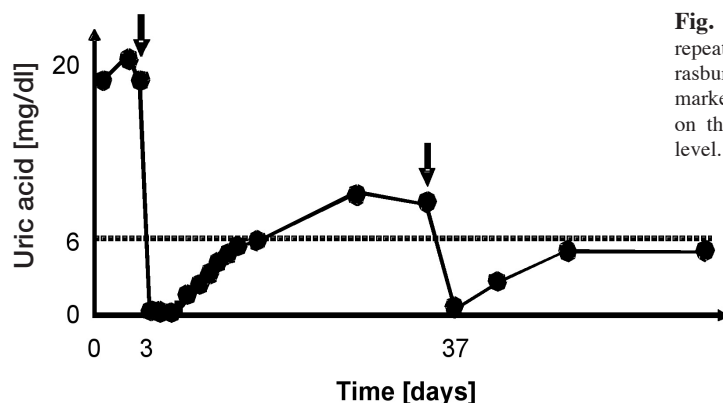


Fig. 2. Influence of repeated infusions of rasburicase (application marked by an arrow) on the serum uric acid level.

rate were increased to 2.5 mg/dl and 110 mm/1st hour, respectively. Rasburicase was once more successfully administered at a dose of 0.1 mg/kg body weight (Fig. 2). Uric acid levels rapidly normalized and arthritic symptoms relieved again after starting prednisone 10 mg daily. Both infusions of rasburicase were well tolerated and no adverse event was observed.

Discussion

This case demonstrates the potent and fast-acting urate-lowering effect of the recombinant urate oxidase, rasburicase, in a critical case of progredient renal insufficiency and coincident acute gouty arthritis. Because of the rapidly progressive course of renal insufficiency, there was a need for urgent intervention in this patient. Therefore, we decided to choose rasburicase as final option to reduce serum uric acid levels, although rasburicase is not approved for the treatment of renal insufficiency. In earlier case reports it was suggested that rasburicase dissolved urate tophi in therapy-resistant tophaceous gout (5, 7). However, rasburicase has no anti-inflammatory effects and the administra-

tion of prednisone is still necessary to control symptoms of arthritis. Rasburicase is indicated to prevent tumour lysis syndrome, but may also be useful in gout patients when allopurinol failed to lower serum urate levels or is contraindicated, as in our case, because of chronic renal failure, allergy or intolerance.

Even though new therapeutic options for the treatment of chronic hyperuricaemia are now arising, the management of the disease in the setting of renal impairment is still unresolved. Febuxostat, a non purine selective inhibitor of the oxidized and reduced form of xanthine oxidase is metabolized in the liver and eliminated predominantly in the stool, thus a possible role for the treatment of gout patients with coexisting renal insufficiency was suggested. Indeed, febuxostat was efficacious in lowering serum urate levels and safe in gout patients with mild and moderate reduced renal function (serum creatinine >1.5 to ≤2.0 mg/dl). However, the small number of treated patients and the exclusion of cases suffering from severe renal insufficiency limit current available data and do not allow a final conclusion concerning safety (8).

In our case, hyperuricaemia and gouty arthritis recurred one month after the first rasburicase administration indicating that continuous urate lowering treatment was necessary. There are only limited data available about re-treatment of rasburicase in patients with gout and renal failure. In a randomised, placebo controlled trial Angelis *et al.* demonstrated that the repeated administration of intravenous rasburicase at a dose of 0.02 mg/kg body weight on 3 to 7 consecutive days depending on initial serum urate levels was well-tolerated and effective in patients with known renal failure (9).

In clinical practice, however, the repeated use of rasburicase is limited by parenteral administration, high costs, possible development of neutralizing antibodies and hypersensitivity reactions as skin rashes (1.4%), urticaria, bronchospasm (>1%), dyspnoea, hypoxemia and anaphylactic shock (>1%). Other adverse reactions are fever (6.8%), isolated neutropenia or in combination with fever (6%), respiratory distress (3%), sepsis (3%), mucositis (2%), nausea (1.7%), vomiting (1.4%), headache (0.9%), diarrhoea (0.9%), and abdominal pain (3). Whether, the pegylated recombinant mammalian urate oxidase, pegloticase, shows a superior tolerability than the repeated application of rasburicase has to be proven in further studies (10).

In summary, rasburicase is useful to rapidly lower urate levels in patients with acute gout and failure of or contraindication to conventional urate lowering drugs. Randomized clinical trials are currently underway to assess the safety and efficacy of rasburicase in patients with chronic gout (9, 11). This case shows that reduction of uric acid levels may also improve renal insufficiency in hyperuricemic patients.

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