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Efficacy of rasburicase therapy in obstructive renal failure secondary to urolithiasis: a novel therapeutic option

P. Segura Torres, F. J. Borrego Utiel, P. Pérez del Barrio, J. M. Gil Cunquero and V. Pérez Bañasco

Department of Nephrology. Complejo Hospitalario de Jaén.

Nefrología 2008; 28 **(1)** 102-105

SUMMARY

The overall incidence of nephrolithiasis-related acute and chronic renal failure is poorly known and surely underestimated. However, obstructive nephropathy represents a potentially curable form of kidney disease that often requires for managing an instrumentation of urinary tract. Rasburicase is an enzyme that transforms uric acid to allantoin, a compound more water soluble that will be excreted by the kidney more easily. Rasburicase has been proven to be an effective therapy for prevention of tumour lysis syndrome. But it also represents an interesting new option in managing hyperuricemia in patients with severe tophaceous gout. We administered rasburicase intravenously (0,20 mg/kg/day, for 2 days) in 2 adults with acute obstructive nephropathy from renal calculi, which was receiving temporary haemodialysis. Rasburicase produced a sharp polyuria 12-18 hours after its administration accompanied with a fast reduction of serum creatinine levels, that returned to normal range without further dialysis. If we suppose that rasburicase can pass through glomerular filter by its relatively low molecular weight, it could disolve tubular uric acid crystals in acute renal failure associated to tumour lysis syndrome, providing the restoration of renal function. But we also could postulate that rasburicase can act in urinary tract, fragmentating renal calculi, promoting relief of obstructive uropathy and the resolution of renal failure. We suggest rasburicase should be tried in this new indication to prove its potential efficacy.

Key words: *Rasburicase. Obstructive acute renal failure. Nephrolithiasis. Uric acid.*

RESUMEN

La incidencia global de la insuficiencia renal crónica o aguda asociada a la litiasis renal es desconocida y probablemente esté infraestimada. Sin embargo, la uropatía obstructiva constituye una causa potencialmente curable de nefropatía que precisa con frecuencia manipulación quirúrgica de la vía urinaria. Rasburicasa es una enzima recombinante que metaboliza el ácido úrico en alantoína, un compuesto más hidrosoluble y fácilmente eliminable por el riñón. Su principal indicación es la prevención de la nefropatía por ácido úrico del síndrome de lisis tumoral. Pero, actualmente, también se considera una posible alternativa al alopurinol en el manejo de la hiperuricemia del paciente con gota tofácea crónica. Presentamos dos casos de fracaso renal agudo anúrico obstructivo provocados por litiasis que precisaron hemodiálisis y a los que se les administró rasburicasa por vía intravenosa (0,20 mg/kg/día durante 2 días). Tras 12-18 horas se observó una poliuria brusca y eficaz que se acompañó de rápida recuperación de la función renal y permitió suspender la hemodiálisis. En virtud del relativo bajo peso molecular de la rasburicasa podemos suponer que es capaz de atravesar el filtro glomerular y aparecer en la orina. Podría así disolver los cristales de ácido úrico formados en el fracaso renal agudo asociado al síndrome de lisis tumoral. Pero también podemos hipotetizar que la rasburicasa actuaría en la vía urinaria fragmentando los cálculos, facilitando su eliminación y liberando la obstrucción, lo que posibilitaría la resolución del fallo renal. Sugerimos que la rasburicasa debería ser ensayada con esta nueva indicación para probar su posible eficacia.

Palabras clave: Rasburicasa. Fracaso renal agudo obstructivo. Litiasis renal. Ácido úrico.

INTRODUCTION

Urate-oxidase is an enzyme that metabolizes uric acid into allantoin, which is more soluble and can be eliminated in the urine. Rasburicase is a recombinant form of the enzyme. It is used to prevent uric acid nephropathy from tumoral lysis syndrome, which appears after tumor treatment, mostly of hematologic nature.[1,2] It produces a rapid decrease of serum uric acid levels, and reduces the amount to be filtered in the kid-

Correspondence: *Pilar Segura Torres*
psegurat@senefro.org
Complejo Hospitalario de Jaén. Avda. del Ejército Español, s/n. 23001 Jaén

ney. That shortens the time of evolution of the renal failure and promotes renal function recovery.[3]

It has been also used in chronic tophaceous gout and the preliminary results seem promising.[4-6] Vogt[4] described a woman with a renal transplant who presented inflammatory tophi in the hands, which were very disabling. After receiving Rasburicase the serum uric acid level returned to normal and the tophi volume was reduced, with no adverse events. Some authors suggest that Rasburicase can be an alternative if allopurinol or benzobromarone are contraindicated[7,8].

Obstructive acute renal failure is very frequent among hospitalized patients, with an incidence of 3.8%.[9] However, the exact incidence of obstructive acute renal failure secondary to lithiasis is unknown, although in some series it is recognized in 3.2% of cases of end-stage renal disease, and the uric acid is the cause of 17.8% of those cases.[10]

If the efficacy of Rasburicase to dissolve uric acid lithiasis were proved, it could allow reducing the size of the stones promoting their elimination. In this way, manipulation of the urinary tract can be avoided and the renal failure resolved.

We present two cases of obstructive acute renal failure with lithiasis that required hemodialysis and that resolved almost immediately after Rasburicase administration.

CASE 1

A 28 year-old male with history of hyperuricemia and intolerance to acetaminophen and non-steroidal anti-inflammatory drugs went to the Emergency Room because of left nephritic colic and hematuria. In the last 36 hours he became anuric. The analytical findings disclosed a mild renal failure (Cr 2.5 mg/dL). The ultrasound investigation showed a left kidney of 17 cm with pelvic, calyx and proximal ureter dilatation, multiple small lithiases within the lower calyx groups and absence of the right kidney. The CT scan confirmed these findings and showed abdominal ureter dilatation. The patient was considered as having an obstructive uropathy due to lithiasis, because of hematuria and lumbar pain. He underwent a ureteral catheterization that was unsuccessful. The anuria persisted and the renal function further deteriorated (Cr 8 mg/dL). A venous catheter was placed and hemodialysis was carried out. Hyperuricemia of 17.6 was detected and a decision was made to treat with Rasburicase (0.20 mg/kg/day) for 2 days. A few hours after the first dose, important polyuria (10 L in 18 hours) developed. In the next days it progressively decreased (fig. 1). Renal function improved dramatically and hemodialysis could be discontinued. Once the clinical picture had resolved, the abdominal CT scan showed neither pelvic nor ureter dilatation

CASE 2

A 70 year-old male is presented with a history of upper gastrointestinal tract bleeding due to bulbar ulceration and hiatal hernia, high blood pressure and right nephritic colic 4 years ago. At that time, he was informed that the left kidney function was suppressed.

A week before admission to the hospital he was treated with non-steroidal anti-inflammatory drugs (meloxicam) because of right nephritic colic. He was evaluated in the Emergency Room for 24 hours for oligo-anuria without fever or hematuria. The blood analysis showed severe renal failure (Cr 7 and urea 167 mg/dL). The ultrasonic study revealed a right kidney of 13.5 cm with lithiasis within the inferior pole and the pelvis (17 and 15 mm, respectively) and absence of the left kidney. The abdominal CT scan confirmed the presence of lithiasis and showed distal ureter dilatation and cortical atrophy of the left kidney (fig. 2). Intravenous fluid therapy and diuretics were initiated but the patient remained anuric. Ureteral catheter placement was tried but it was unsuccessful and nephrostomy was not indicated because of insufficient pelvis dilatation. Hemodialysis was carried out after placing a central line. Despite fluid administration an increase in urinary tract dilatation was not observed and ~~a~~ percutaneous nephrostomy could not be performed. In this setting the decision to administer Rasburicase (0.20 mg/kg/day) for 2 days was made. Six hours after the beginning of the therapy the

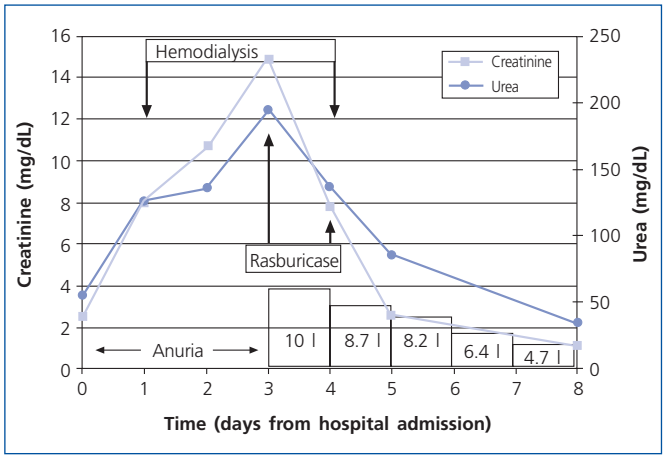

Figure 1. Case 1: Evolution of renal function and diuresis after Rasburicase [the squares show the diuresis (L/24-h)].

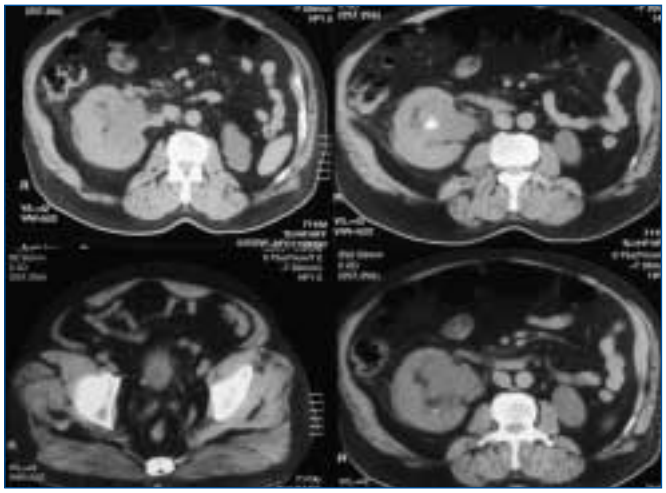

Figure 2. Top left: dilation of the right renal pelvis. Atrophic left kidney. Top right: calcium-containing stone within the pelvis. Bottom left: calcium-containing stone within the ureteral meatus. Bottom right: calcium-containing stone at the inferior pole.

diuresis was recovered. The patient presented polyuria (6 L in the first night) that progressively decreased in the next days. The renal function improved very fast and hemodialysis could be discontinued (fig. 3). A few days later the abdominal CT scan showed the disappearance of the lithiasis within the right ureter.

DISCUSSION

Renal disease produced by uric acid can be due to lithiasic urinary tract obstruction, to intra-tubular precipitation of uric acid crystals (in case of overproduction as in tumoral lysis syndrome) or to interstitial nephropathy (as in hyperuricemic nephropathy). Besides, uric acid stones usually contain a uric core frequently covered by deposition of calcium oxalate crystals, which favors the growth of the calculi and modifies the radiological characteristics.

Making the differential diagnosis between them requires bringing together the underlying pathology of the patient, the clinical setting in which it occurs, the radiological findings, the analytical parameters, and the clinical progression itself observed during the recovery phase of renal damage.

In both cases there was a high suspicion of obstructive renal failure, because of sudden anuria, hematuria and lumbar pain (case 2), urinary tract dilatation, and lithiasis images, and especially the rapidity and pace of restoration of the diuresis. In both cases we were witnesses of the abrupt reappearance of the diuresis, which clearly reminds the release of the urinary tract after short-termed obstruction, accompanied by a reduction in ureteral dilatation in radiological images, which supports the diagnosis of acute obstructive renal failure.

In case 1 very high serum levels of uric acid were detected. Therefore it could be hypothesized that the acute renal failure was due to intra-tubular uric acid precipitation. However, in cases of uric acid precipitation the renal function recovery is slow, the diuresis volumes grow progressively and the serum levels of the nitrogenous products also decrease gradually. On the contrary, in the presented patient the recovery was very abrupt.

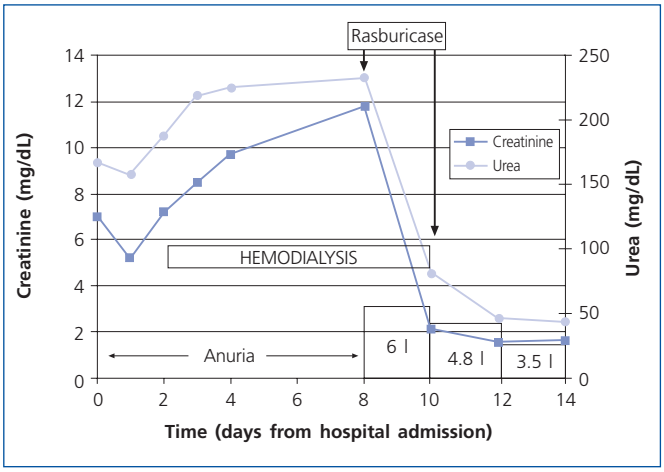

Figure 3. Case 2: Evolution of renal function and diuresis after Rasburicase [the squares show the diuresis (L/24-h)].

The clear and surprising temporal relationship between the administration of Rasburicase and the reappearance of the diuresis can be a clue to understand the underlying mechanism for the renal failure resolution. We cannot be sure of the nature of the stones but it is possible that they were composed of uric acid. First, they could not be seen in the plain X-ray film. Second, in case 1, there was hyperuricemia and the possibility that the stone was of uric acid seems likely. Besides, in case 2 the lithiasis could be mixed in nature with a uric acid core. We postulate that Rasburicase reduced the stone size enough to allow it moving and passing through the narrowest part, which is the distal ureter.

Rasburicase must be able to reach the urinary tract passing through the glomerular filter to be efficacious. Sixty percent of the proteins present in the urine are of plasmatic origin and that means that they are able to cross this barrier.[11] The permeability of the filtration membrane depends on the charge, the size and the form of the molecule, and each one has a characteristic glomerular sieving coefficient. Many studies have shown that the albumin, with a molecular weight of 69 kDa, does not cross the glomerular filter,[12] although it can actually be detected in the urine in very small quantities (15-20 mg/kg in females and 18-25 mg/kg in males). Norden[13] measured the sieving coefficient of 12 plasmatic proteins in humans and found a clear relation with the molecular weight. The α_1-microglobulin with a weight of 31 kDa had a greater coefficient than the albumin. That allows hypothesizing that Rasburicase, with a molecular weight of 34 kDa, can be present in the urine.

Therefore, Rasburicase is theoretically able to pass through the glomerular filter and be eliminated in the urine in a significant quantity. In this way it acts on intra-tubular uric acid, dissolves the crystals and promotes their elimination. This mechanism helps to shorten the evolution of the acute established renal failure in case of tumoral lysis syndrome.[3,14] We also hypothesize that Rasburicase can reach the urinary tract and dissolve the stones with a uric acid component within the calyces, pelvis and ureter, favoring their elimination. If the capability of Rasburicase to dissolve uric acid stones is confirmed either *in vitro* or *in vivo,* the direct administration of the drug in the urinary tract through nephrostomy catheters could be a new therapeutic approach in patients with this common pathology.

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