Use Of Rasburicase In The Treatment of Hyperuricemia In A Hydropic Infant

Yeşim Coşkun1, Utku Demirel2, İpek Akman1

1 Bahcesehir University, Göztepe Medical Park Hospital, Department Of Pediatrics
2 Yakacık State Hospital

Abstract

Hyperuricemia is a common metabolic derangement seen in acute kidney injury and tumor lysis syndrome. The standard treatment of hyperuricemia is hydration, urinary alkalinization and allopurinol administration. Rasburicase is a recombinant urate oxidase that effectively oxidizes uric acid to allantoin which is readily excretable through urine. We reported a female infant who was born at 37th gestational week by repeat caesarean section with hydrorps fetalis. The maternal blood type was 0, Rh-negative. Infant’s blood type was 0, Rh-positive. The initial Hgb: 6.2 g/dl and direct Coombs was +4. She had evidence of multiorgan failure. On the third hospital day, she had oliguria, serum creatinine level was 2.1 mg/dl and uric acid level was documented 23.7 mg/dl despite allopurinol administration and rasburicase infusion 0.2 mg/kg was commenced. The next day uric acid level was 13 mg/dl and a second dose of rasburicase was given. On the following day uric acid level declined to 2 mg/dl. After continuous furosemide infusion was begun urinary output had improved to 1.5 ml/kg/hr. However she had intracranial bleeding and died of multiorgan failure on the 10th day of life. To our knowledge, it was the first hydropic infant whose hyperuricemia was treated with rasburicase.

Keywords: Hydrops Fetalis; Hyperuricemia; Rasburicase

Özet

Akut böbrek yetmezliği ve tümör lizis sendromunda sıkça görülen bir metabolik bozukluk olan hiperüriseminin standart tedavisi hidrasyon, alkalinizasyon ve allopürinol uygulamasından oluşmaktadır. Rasbürikaz, ürik asitin idrarla kolaylıkla atılabilen bir metabolit olan allantoine etkin bir şekilde okside edilmesini sağlayan, rekombinant bir urat oxidazdır. 37. gebelik haftasında sezaryen ile doğan hidrops fetalisli bir bebeği rapor etmeyi amaçladık. Anne kan grubu 0 Rh-negatif, bebek kan grubu ise 0, Rh-pozitif idi. İlk hemoglobinin değeri 6.2 g/dl ve direkt Coombs +4’ti. Fizik muayenesinde multiorgan yetmezliği bulguları vardı. Yatışının 3. gününde bebekte oligüri gelişti; serum kreatinini 2.1 mg/dl ye ve ürik asit değeri de 23.7 mg/dl ye yükseldi. Allopürinol tedavisinden yanıt alınamayan rasbürikaz tedavisi 0.2 mg/kg dozunda başlandı. Dördüncü gün ürik asit düzeği 13 mg/dl ye indi ve ikinci doz rasbürikaz tedavisi sonrası 5. gün ürik asit 2 mg/dl ye kadar düştü. Ayrıca dönemde başlanan devamli furosemid infüzyonu sonrası idrar çıkışı 1.5 ml/kg/hr e kadar yükseldi. Hasta hayatının 10. gününde intrakranial kanama ve multiorgan yetmezliği nedeniyle kaybedildi. Bu vaka rasbürikaz tedavisi alımda bulunan ilk hiperürisemik hidrops fetalis vakasıdır.

Anahtar Kelimeler: Hidrops Fetalis; Hiperürisemi; Rasbürikaz
Introduction
Uric acid, a weak organic acid, is the end-product of purine metabolism in humans. It is poorly water-soluble at acidic pH. Plasma uric acid level depends on de novo purine synthesis, catabolism of tissue nucleic acids, increased turnover of preformed purines and to a lesser extent on dietary intake. Uric acid is eliminated by gastrointestinal, biliary and renal excretion. Hyperuricemia is defined as uric acid levels over 8 mg/dl. Hyperuricemia is notorious for its detrimental effects on kidneys, brain and joints. Since kidneys are the main site of uric acid excretion, urate crystals precipitating in hyperuricemic states may potentially lead to uric acid calculi. In some instances when hyperuricemia is rapid and relentless, renal urate handling mechanisms are overwhelmed, urate precipitates and obstructs tubules of distal nephron, where pH is acidic. Unless treated promptly this may lead to acute urate nephropathy and acute renal failure. The standard treatment of hyperuricemia is hydration, urinary alkalinization and allopurinol administration. Allopurinol, inhibiting xanthine oxidase, blocks de novo formation of uric acid.

Rasburicase is a recombinant urate oxidase that effectively oxidizes uric acid to allantoin which is highly water-soluble thus readily excretable through urine. Rasburicase has proven to be an effective and safe uric acid lowering agent used in the treatment of tumor lysis syndrome in adults and children with hematologic malignancies. It is reported that rasburicase is a more potent and faster-acting hypouricemic agent compared to oral allopurinol. In a case series, Hobbs et al. concluded that single intravenous infusion of rasburicase is very effective in diminishing uric acid levels in patients with acute kidney injury due to various insults. (such as HIE, sepsis, severe dehydration etc.)

Hydrops fetalis is a severe and almost invariably lethal condition. It is a pathologic accumulation of fluid in the skin and one or more other body compartments of the fetus, including the pleural space, peritoneal cavity, pericardial sac, or placenta. Most commonly recognized for its immune causes, such as Rh isoimmunization, with the advent of Rho (D) immunoglobulin nonimmune causes (congenital infections, cardiac arrhythmias and anomalies, genetic abnormalities etc.) becomes more prominent.

We aimed to present our experience with rasburicase infusion in a neonate with immune hydrops fetalis and multi-organ failure who had hyperuricemia due to acute renal failure and severe hemolysis.

Case
A female infant was born at 37th gestational week from non-consanguineous parents after an uneventful pregnancy with elective caesarean section. The mother attended antenatal visits irregularly nevertheless these visits were without positive clinical findings. Apgar scores were 3 and 7 at 1 and 5 minutes of life, respectively. Her birth weight was 3150 gr. The mother was 32 years old (gravida 3, para 3). The maternal blood type was 0, Rh-negative. Rhogam was administered after the first pregnancy. First sibling is a 7 year-old healthy girl. Second pregnancy resulted in fetal demise at 38 weeks of gestation. At birth amniotic fluid was meconium stained and the baby was depressed, pallid and in severe respiratory distress. Delivery room resuscitation with endotracheal intubation and positive pressure ventilation resulted in rapid improvement.

On arrival intravenous fluids were started and the infant was mechanically ventilated on SIMV mode. Her oxygen saturati-
ons ranged between 75-85 %. Blood gas values reached the physiologic range with high ventilator parameters at eight hours of age. Chest x-ray revealed cardiomegaly and poor aeration of the lungs. Dopamine and dobutamine and adrenalin infusions were commenced shortly after her admission however, the patients blood pressure was normalized after hydrocortisone administration. Hydration and urinary alkalinization was continued and hyperkalemia was treated with calcium gluconate, nebulized ventolin and oral anti-potasyum (kayexalate). Severe hypoglycemia was brought under control with glucose infusion rates of 12 mg/kg/min. Treatment with iv ampiilin and netilmicine was begun after blood and urine cultures were obtained. Preexchange G6PD and methemoglobin levels were normal. Initial blood biochemistry revealed the following: BUN:10.7, Creatinin: 0.75, AST:4202, ALT:784, glucose: 20, Na: 148, K:7.6, Calcium:12,1.

After the second exchange transfusion was performed with whole blood, IVIG was administered. The patient had endotraheal bleeding and hematuria on admission. Coagulation studies revealed a prothrombin time of: 85 seconds, aPTT: 66.2 seconds, INR: 12.1 and fresh frozen plasma was begun four times a day. Ranitidine infusion was given due to upper gastrointestinal bleeding.

Transthoracic echocardiographic examination revealed dilated left heart chambers, ejection fraction of 31 %, pulmonary hypertension and a wide PDA. Sildenafil citrate treatment was started.

On the second hospital day, creatinin level increased to 1.4 mg/dl and netilmicine, due to its nephrotoxicity, was replaced by cefepime. Allopurinol was started because serum uric acid level was documented 9 mg/dl. Renal ultrasonographic examination showed increased echogenicity of kidney parenchyma bilaterally. Packed red blood cells were administered to treat anemia, in addition hypoalbuminemia was treated with albumin infusion.

On the third hospital day, serum creatinin level was 2.1 mg/dl and uric acid level was documented 23.7 mg/dl despite allopurinol administration for this reason rasburicase infusion 0.2 mg/kg was commenced. Oliguria refractory to continuous furosemide infusion, lack of postnatal physiologic diuresis and infant’s continuous weight gain indicated renal failure which necessitated peritoneal dialysis. Dialysis catheter insertion was planned, however the infant’s bleeding diathesis which comprised active bleeding form venipuncture sites impeded the operation for catheter placement. Fresh frozen plasma, packed red blood cells and platelets were given in an effort to stabilize the patient before insertion of peritoneal dialysis catheter however, bleeding diathesis did not subside. Despite every effort the patient’s hypervolemic state did not resolve and her weight gain was continuous.

On the fourth hospital day, control echocardiography revealed that ejection fraction improved (69 %). Transfontanel ultrasonography showed a hematoma, that caused a minimal shift, adjacent to lateral ventricle. Dimensions of hematoma were 35x28 mm. Second dose of rasburicase was given because uric acid level was13mg/dl. On the following day uric acid level declined to 2 mg/dl. After continuous lasix infusion was begun urinary output had improved to 1.5 ml/kg/hr. Due to on going gastrointestinal hemorrhage sucralflate treatment was added to ranitidine infusion. Intracranial hematoma was consulted to neurosurgery department. Because of high serum ammonia level that increased up to 535, Na benzoate infusion was given.

On the seventh hospital day blood count revealed neutopenia. One dose of G-CSF was given and antibiotics were changed to vancomycine and meropenem.

On the tenth hospital day, blood pressure began to decline. Despite every supportive effort for profound hypotension, metabolic abnormalities and intracranial hemorrhage, she died of multiorgan failure.

Discussion
The etiology of acute renal failure in newborn population is diverse. It most commonly is due to renal hypoperfusion and renal hypoxic ischemic insult. Whatever the cause, hyperuricemia is a common metabolic derangement seen in acute kidney injury. It is recently documented that uric acid per se may independently increase the risk of chronic renal disease and aggravate preexisting nephropathy. The conventional
The treatment of hyperuricemia have been limited to allopurinol, hydration and urinary alkalinization. Allopurinol, inhibiting xanthine oxidase, blocks uric acid formation but increases plasma concentrations of hypoxanthine and xanthine which are nephrotoxic. Furthermore, allopurinol has no effect on preexisting plasma uric acid molecules.

Rasburicase is a recombinant urate oxidase that effectively oxidizes uric acid to allantoin which is about five times more water-soluble than hypoxanthine and xanthine, thus readily excretable through urine. It is widely used in the treatment of hyperuricemia due to tumor lysis syndrome in both adult and pediatric population. Hobb et al. reported a case series of infants with acute kidney injury due to various insults. They found that one-time, single, intravenous bolus of rasburicase was effective in reducing serum uric acid levels. They reported no adverse effects. Stanton et al. reported the efficacy of rasburicase compared to allopurinol in lowering plasma uric acid in children with leukemia or lymphoma at high risk for developing tumor lysis syndrome. They documented that rasburicase was a more potent and faster-acting hypouricemic agent than oral allopurinol. Safety profiles of two drugs did not differ significantly. Moreover, the incidence of renal failure requiring renal replacement therapy (dialysis or hemofiltration) was null in the rasburicase group compared to one patient in the allopurinol group. Rasburicase can not be used in patients with glucose-6-phosphate dehydrogenase deficiency due to increased risk of hemolysis. Allergic reactions and methemoglobinemia are other potential side effects of rasburicase treatment.

In our patient hyperuricemia was secondary to both acute renal failure and hemolysis. Standart treatment with allopurinol, hydration and urinary alkalinization was ineffective so that two doses of rasburicase was administered with an excellent response. No rebound hyperuricemia was observed 24 hours after cessation of infusion. Serum creatinine levels and urinary output improved significantly after two rasburicase infusions. Infant’s methemoglobin and G6PD levels were normal. No allergic side effects and cyanosis were observed during and after the IV rasburicase infusions. However, the infant died of multiorgan failure and intracranial hemorrhage on the 10th day of life.

Hydrops fetalis is one of the most catastrophic events a neonatologist may encounter during routine practice. Rh sensitization can almost always be prevented by the administration of Rh immunoglobulin to an Rh-negative women at 28 weeks of gestation and again within 72 hours of delivery of an Rh-positive infant. In her first pregnancy the mother was sensitized despite Rhogam administration. The second baby most possibly had died of hydrops fetalis. Due to inadequate follow-up the patients missed the chance of intruterine transfusion and was born in a very poor condition. In this report, we aimed to discuss a case of hydrops fetalis with hyperuricemia who was treated with rasburicase. Rasburicase was effective and well-tolerated by the patient. Thus, it is an agent that rapidly controls plasma uric acid level in neonates with hyperuricemia due to hydrops fetalis and acute renal failure.