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Reversal of Severe Volume Deplete Acute Kidney Injury by Rasburicase

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ABSTRACT

We report on a case of acute kidney injury in a patient with severe volume depletion from high ileostomy output and poor oral intake associated with hyperuricemia and hyperkalemia. The patient presented with similar features on three separate admissions. A conservative management approach was undertaken that included infusion of rasburicase, since the patient refused to undergo hemodialysis on each occasion. Rasburicase is a recombinant urate oxidase enzyme that converts uric acid to allantoin which is five to ten times more soluble than uric acid in urine, thereby enhancing urinary excretion. Rasburicase was administered each time and was followed by a prompt increase in urine output, rapid decrease in serum uric acid level, and recovery of renal function without the need for acute renal replacement therapy. We believe that rasburicase, with a molecular weight of 34 kDa, crossed the glomerular filtration barrier and entered the tubular fluid where it dissolved intra-tubular uric acid, thus relieving obstruction, thereby rapidly enhancing urine excretion and improving renal function. Based on this experience, we propose that rasburicase offers an alternative treatment for acute kidney injury in similar types of settings. To the best of our knowledge this is the first reported case in this situation.

Keywords: Acute Kidney Injury; Rasburicase; Hyperuricemia; Ileostomy

1. Introduction

Patients with ileostomies can acutely develop high volume output states that may be associated with acute kidney injury and life threatening electrolyte and acid base disorders [1]. Traditionally this is treated with intravenous fluid and if indicated, hemodialysis. We report a case where high ileostomy output resulted in severe volume depletion, acute kidney injury, and marked hyperuricemia on three separate occasions. On all three occasions the patient adamantly refused to undergo hemodialysis. Rasburicase, a recombinant urate oxidase enzyme [2] was administered on each of these occasions and was followed by a prompt increase in urine output, rapid decrease in serum uric acid level, and recovery of renal function. We submit that rasburicase administration was responsible for the described course of events and should be considered as an alternate approach to management of acute kidney injury in similar clinical settings.

2. Case Report

A 59 year-old woman presented to the emergency room with nausea, vomiting and fatigue. She reported increased ileostomy output and decreased urine output. Her past medical history was significant for type 2 diabetes mellitus, hyperlipidemia and chronic obstructive airway disease. She had undergone right nephrectomy in 1995 for obstructive nephrolithiasis. Four months prior to this presentation she underwent a total abdominal hysterictomy and bilateral salpingo-ooperectomy for stage 1 A endometrial adenocarcinoma. Her hospital course was complicated by bowel perforation requiring partial ileal resection and ileostomy. Since creation of the ileostomy the patient has had two similar episodes described below, requiring admission to the hospital.

Six weeks prior to the current admission she presented to the emergency room with a 3 day history of nausea, vomiting, high ileostomy output, poor oral intake, and diminished urine output for one day. She denied fever, chills or abdominal pain. Her medications included pioglitazone, pravastatin, fenofibrate, aspirin, tiotropium and astelin nasal spray. Her admission blood pressure was 93/61 mmHg, heart rate 88 beats a minute and regular, temperature 35.9˚C and respiratory rate 16 breaths /min. Her oral mucous membranes were dry. The ileostomy was intact. Initial laboratory data revealed serum sodium (Na^+) 128 mEq/L(128 mmol/L), potassium (K^+)

7.0 mEq/L (7.0 mmol/L), chloride 82 mEq/L (82 mmol/L), and bicarbonate 30 mEq/L (30 mmol/L). Blood urea nitrogen (BUN) was 146 mg/dl (52.1 mmol/L), serum creatinine (SCr) 11.2 mg/dl (990.1 umol/L) (from a baseline value of 0.7 mg/dl, 61.9 umol/L), phosphorus 16.5 mg/dl (5.3 mmol/L), and uric acid 24.4 mg/dl (1.45 mmol/L). No significant abnormalities were noted on EKG. An abdominal computed tomography (CT) scan revealed a kidney on the left with mild perinephric stranding and prominence of the collecting system, without hydronephrosis. She received 2.7 liters of normal saline intravenously and voided30cc/hr of urine. Hemodialysis was offered but the patient adamantly refused. At this point she received rasburicase 7.5 mg intravenously over 30 minutes (0.08 mg/kg/dose). Her urine output increased to 1300 cc (approximately 130 ml/hr) over the next 10 hours. Fifteen hours following rasburicase infusion, serum K^+ decreased to 3.1 mEq/L (3.1mmol/L), BUN declined to 116 mg/dl (41.4 mmol/L) and SCr 8.67 mg/dl (766.4 umol/L). The serum uric acid level had decreased to 5.4 mg/dl (0.32 mmol/L) within 24 hours. White blood cell count decreased from an admission value of $7.1 \times 10^3/mL^3$ to $2.1 \times 10^3/mL^3$and spontaneously recovered. The patient was continued on intravenous hydration throughout her ten day hospital stay. Her ileostomy output decreased with diphenoxy/atropine. She was discharged home with a SCr of 1.27 mg/dl (112 umol/L).

Two weeks later, routine laboratory tests revealed a serum of Na^+ 123 mEq/L (123 mmol/L), K^+ 8.5 mEq/L (8.5 mmol/L), chloride 88 mEq/L (88 mmol/L), bicarbonate 21 mEq/L (21 mmol/L), BUN 80 mg/dl (28.6 mmol/L) and SCr 6.37 mg/dl (563.11 umol/L). The patient was again hospitalized with symptoms of nausea, vomiting, decreased oral intake and high ileostomy output. Vital signs revealed blood pressure 104/73mmHg and heart rate 112 beats/min. The physical exam was significant for dry mucous membranes. Repeat laboratory data revealed serum Na^+ 130 mEq/L (130 mmol/L), K^+ 8.0mEq/L (8.0 mmol/L), chloride 88 mEq/L (88 mmol/L), bicarbonate 21 mEq/L (21 mmol/L), SCr 6.30 mg/dl (556.9 umol/L), phosphorus 6.6 mg/dl (2.1 mmol/L), and uric acid 12.1 mg/dl (0.72 mmol/L). Renal sonogram showed the single left kidney with no evidence of hydronephrosis. She was given 2 liters of intravenous normal saline along with three doses of sodium polystyrene sulfonate (30 gm) over4 hours. No increase in urine output was noted. The patient again refused hemodialysis. Rasburicase 11.5 mg (0.13 mg/kg/dose)was infused over 30 minutes. Urine output increased to 920 ml over the next 24 hours. Fifteen hours post rasburicase infusion, serum K^+ was 4.8 mEq/L (4.8 mmol/L), BUN 66 mg/dl (23.6 mmol/L) and SCr 6.23 mg/dl (550 umol/L). Serum uric acid level had decreased to 1.8mg/dl (0.11 mmol/L). Neutropenia evolved which required a single subcutaneous dose of filgastrim (Neupogen) 300 microgram. The patient was discharged after a 7 day hospital stay with a SCr of 1.56 mg/dl (137.9 umol/L) and a normal white blood cell count.

On the current admission, blood pressure was 113/68 mmHg, heart rate 113 beats/min, temperature 35.4˚C, and respiratory rate 18 breaths/min with O_2 saturation of 98% on room air. Mucous membranes were dry. Cardiovascular, pulmonary and neurological examinations were unremarkable. Abdominal examination revealed an intact ileostomy, no tenderness, and normal bowel sounds. Laboratory tests showed serum Na^+ 132 mEq/L (132 mmol/L), K^+ 8.1mEq/L (8.1 mmol/L), chloride 95 mEq/L (95.0 mmol/L), bicarbonate 17 mEq/L (17.0 mmol/L), SCr 8.0 mg/dl (707.2 umol/L), phosphorus 7.2 mg/dl (2.3 mmol/L) and uric acid 18.6 mg/dl (1.1 mmol/L). The renal sonogram was unchanged. The patient was given three doses of sodium polystyrene sulfonate (30 gm), and calcium gluconate 1 gm and 50% dextrose (15 gm) and 10 units of regular insulin intravenously. Five liters of normal saline were infused over the initial 24 hours with no urine output. She again refused hemodialysis. A single intravenous dose of rasburicase 6 mg (0.08 mg/kg/dose) was given. Within 24 hours, the urine output increased to 50ml/hr and serum chemistry showed K^+ 3.2 mEq/L (3.2 mmol/L), BUN 76 mg/dl (27.1 mmol/L), SCr 6.67 mg/dl (589.6 umol/L) and uric acid of 4.7 mg/dl (0.28 mmol/L). The white blood cell count decreased from $6.4 \times 10^3/mL^3$ to $2.5 \times 10^3/mL^3$and recovered spontaneously. She continued to receive intravenous hydration until her sixth hospital day at which point she underwent reversal of the ileostomy. The patient was discharged home 1 month later with a SCr of 0.83 mg/dl (73.4 umol/L).

3. Discussion

We report on a case of acute kidney injury in a patient with severe volume depletion from high ileostomy output associated with hyperuricemia and hyperkalemia on three separate admissions. A conservative approach was taken in keeping with the patient's refusal to undergo hemodialysis on each occasion. Administration of rasburicase was followed by a dramatic decrease in serum uric acid level, with a concomitant increase in urine output and significant improvement in renal function on each occasion, alleviating the need for hemodialysis. We submit that rasburicase was responsible for this course of events.

Acute urate nephropathy is most commonly encountered in patients with large tumor burdens who undergo chemotherapy and where there is rapid destruction of tumor cells, the so called "tumor lysis syndrome" [3]. Very elevated serum uric acid levels contributing to acute renal failure has also been described in young in-

fants after cardiovascular surgery [4], and has also been proposed as a risk factor for acute kidney injury in adult patients undergoing high risk cardiac surgery [5,6]. A rise in serum uric acid is also seen in toxic and ischemic acute kidney injury where it is thought to be the result of both increased generation and decreased excretion of uric acid [7]. In all of these settings there is reason to invoke the elevated serum uric acid in the pathogenesis of acute kidney injury.

A number of mechanisms have been proposed by which uric acid may contribute to acute kidney injury. First, the markedly elevated serum uric acid level results in supersaturation of the tubular fluid with precipitation of uric acid and obstruction of the tubular lumina. From micro puncture studies it is known that uric acid precipitates mainly in the distal tubule where uric acid concentration is high and the environment is acidic [8]. Indeed precipitation of uric acid was also noted in the vasa rectae [8]. Second, in an animal model, hyperuricemia has been shown to cause renal vasoconstriction, characterized by a marked increase in resistance primarily of the afferent arteriole [9]. The mechanism by which this occurs appears to be a suppression of nitric oxide production since vasoconstriction can be reversed with L-arginine [10]. Third, uric acid has been shown to stimulate an inflammatory response in vascular smooth muscle cells via proinflammatory cytokines such asMCP-1 [11] Whether any of these mechanisms play a role in acute kidney injury associated with severe volume depletion as described herein, remains to be determined.

Patients with well-functioning ileostomies under steady state conditions can have a 7% to 11% decrease in total body sodium and water [12] reflecting a stable, modest fluid depleted state. With increased ileostomy output and the attendant volume depletion, these individuals can develop sudden acute electrolyte and acid-base disorders [1]. Most commonly, and as observed in our patient, metabolic acidosis ensues due to the high bicarbonate content of the ileostomy fluid. The associated hyperkalemia can be explained by the acute drop in glomerular filtration rate. A paucity of data exists regarding uric acid levels in this setting. In this regard Adler and coworkers [13]reported a series of 133 dehydrated children under the age of 4 years admitted with diarrhea. The majority of children and infants (80%) had transient hyperuricemia that correlated with the serum urea nitrogen level, with a mean serum uric acid level of 12.3 mg/dl (0.73 mmol/L), and range of 2.3 mg/dl (0.14 mmol/L) to 38.0 mg/dl (2.26 mmol/L). Most children had urate crystals in their urine. With volume repletion, uric acid levels returned to normal.

Rasburicase is a recombinant urate oxidase enzyme that converts uric acid to allantoin which is five to ten times more soluble than uric acid in water, thereby enhancing urinary excretion of this product of nucleic acid degradation [2]. Rasburicase, with a molecular weight of 34 kDa, can cross the glomerular filtration barrier and enter the tubular fluid where it can carry out its intended effect [2]. Rasburicase has been reported to be effective in the treatment of renal failure due to obstructive uric acid stones [14]. Both patients in that report did not show any improvement in renal function with intravenous fluid and hemodialysis; rasburicase infusion resulted in brisk diuresis and renal recovery within 24 hours. Repeat abdominal CT scans after rasburicase therapy confirmed complete resolution of uric acid stones with no obstructtion to the urinary tract [14]. A successful outcome following the use of rasburicase has now been reported in an anuric pediatric patient with hyperuricemia in the setting of the hemolytic uremic syndrome [15], and in two teens with acute kidney injury secondary to rhabdomyolysis caused by ecstasy intoxication [16]. In all these settings and now in the patient we report, rasburicase most likely dissolved intra-tubular uric acid, thus relieving obstruction, thereby rapidly enhancing urine excretion and improving renal function.

Acute kidney injury associated with hyperuricemia is traditionally treated with volume expansion and urinary alkalization which favors solubilization of uric acid to urate in the urine. This helps to relieve intra-tubular obstruction. This is based on animal studies where high tubular fluid flow, whether induced by solute or water diuresis, was the primary mechanism of protection in acute urate nephropathy, with alkalization playing a lesser role [17]. Rasburicase rapidly lowers serum uric acid by converting it to a soluble compound allantoin, thereby dramatically decreasing proximal tubular uric acid excretion and preventing its precipitation in the tubular lumen. This mechanism probably holds true both in acute kidney injury related to marked hyperuricemia, and the tumor lysis syndrome (TLS). In addition, rasburicase is freely filtered at the level of the glomerulus and enters the tubular fluid where it can dissolve uric acid crystals and relieve intra tubular obstruction. This ameliorates acute kidney injury associated with acute uric acid nephropathy. Hemodialysis is a treatment of choice in patients with volume overload and hyperkalemia associated with severe hyperuricemia. If there are relative contraindications for access placement such as a severe bleeding disorder and/or refusal by a patient, rasburicase may offer an alternative therapeutic choice as demonstrated in our patient.

In conclusion, we report on a case with acute kidney injury associated with high ileostomy output and secondary hyperuricemia which responded to rasburicase infusion. On three separate occasions, rasburicase infusion led to a dramatic decrease in serum uric acid level over a short period of time, with rapid improvement in renal

function. Hemodialysis was obviated in keeping with the patient's request. Based on this limited experience, we propose that rasburicase offers an alternative treatment for acute kidney injury in similar types of settings. Additional clinical studies are needed to confirm this observation.

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