

Type 4 Renal Tubular Acidosis Induced by Spironolactone

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Spironolactone, an aldosterone antagonist with diuretic and antihypertensive properties, has long been considered a second-line therapy in the treatment of congestive heart failure, essential hypertension, and hypokalemia.¹ However, new evidence has emerged, making spironolactone part of the standard therapeutic regimen for congestive heart failure.² Along with this new indication has come a rapid escalation in the use of the medication, especially among patients over 65 years of age.

These events have also led to the elucidation of spironolactone's side effects. It is well known that spironolactone can cause hyperkalemia, especially if simultaneously administered with an angiotensin-converting enzyme inhibitor and/or nonsteroidal anti-inflammatory drugs. Other recognized side effects of spironolactone include diarrhea and hyperchloremic metabolic acidosis, especially in patients with a prior history of renal insufficiency.³ A few case reports have been published discussing type 4 renal tubular acidosis (RTA) developed by patients while taking spironolactone.^{4,5} This article presents the case of a 71-year-old woman who developed severe hyperkalemia and type 4 RTA following a short course of spironolactone therapy.

CASE PRESENTATION

Initial Presentation and Management

A 71-year-old woman presented to the hospital with a 3-week history of lethargy, nausea, and diarrhea. Her medical history included hypertension, congestive heart failure, atrial fibrillation, chronic obstructive pulmonary disease, and gout. Her medications were enalapril 5 mg, digoxin 0.25 mg, furosemide 40 mg, diltiazem 180 mg, allopurinol 300 mg, colchicine 0.6 mg twice daily, warfarin 5 mg, and spironolactone 200 mg once daily started 1 month prior to admission. The patient was admitted to the hospital for dehydration along with hyperkalemic, hyperchloremic metabolic acidosis, which was caused by combined renal

and gastrointestinal effects of spironolactone. Her serum potassium level was 6.8 mEq/L (normal, 3.5 to 5.0 mEq/L), serum bicarbonate was 11 mEq/L (normal, 22 to 28 mEq/L), serum chloride was 114 mEq/L (normal, 98 to 107 mEq/L), anion gap was 12 mEq/L (normal, 6 to 13 mEq/L), and serum creatinine was 2.5 mg/dL (normal, 0.6 to 1.2 mg/dL), increased from a baseline value of 1.1 mg/dL. The spironolactone therapy was discontinued, and the patient's management consisted primarily of administration of fluids and sodium polystyrene sulfonate. The patient was discharged to home 2 days later when her serum potassium and creatinine levels decreased. Results of stool studies were negative for fecal leukocytes, ova and parasites, and *Clostridium difficile* toxin. The patient's serum bicarbonate level remained low (12 mEq/L) at discharge.

Subsequent Presentation, Evaluation, and Management

The patient returned to the hospital 18 days later with the same symptoms of lethargy, nausea, and diarrhea. Physical examination revealed an obese African American woman with a pulse of 103 bpm and a blood pressure of 125/58 mm Hg. Results of a test for orthostatic hypotension were negative, although skin turgor was reduced. The patient's heart rhythm was irregularly irregular with no murmurs. Auscultation of the chest revealed bilateral basal crackles and scattered wheezes. The abdomen had normal active bowel sounds with no rebound or guarding but did exhibit mild diffuse

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tenderness on palpation. The patient had bilateral clubbing of the extremities, but no edema.

Laboratory evaluation on the patient's second hospital admission revealed the following values: serum potassium, 7.2 mEq/L; serum bicarbonate, 14 mEq/L; serum chloride, 104 mEq/L; anion gap, 21 mEq/L; and serum creatinine, 4.2 mg/dL. Arterial blood gas analysis demonstrated a pH of 7.20 (normal, 7.35 to 7.45) and a P_{CO_2} of 27 mm Hg (normal, 32 to 48 mm Hg). This presentation was consistent with an increased anion gap acidosis secondary to acute renal failure. Repeat stool studies were again negative for fecal leukocytes, ova and parasites, and *C. difficile* toxin.

The patient was given fluids to treat her dehydration, sodium polystyrene sulfonate to treat her hyperkalemia, and sodium bicarbonate to treat her acidosis. Despite the resolution of diarrhea and correction of renal function during her hospital stay, the patient maintained a persistent hyperchloremic, non-anion gap metabolic acidosis. Her serum bicarbonate level stabilized at 14 mEq/L and serum chloride at 114 mEq/L, with an anion gap of 12 mEq/L. The patient was discharged with this hyperchloremic acidosis but was not compliant with follow-up. When she returned to the clinic after several months, the metabolic abnormalities had cleared.

DISCUSSION

Adverse Effects of Spironolactone

Spironolactone has been associated with the escalation of existing renal insufficiency, hyperkalemia, dehydration, and type 4 RTA. Other reported complications include gastric bleeding, diarrhea, change in mental status, ataxia, and rare cholestatic/hepatocellular toxicity.⁶ The potentially detrimental effect of spironolactone treatment on renal function is particularly evident in elderly patients.^{4,5}

Renal Tubular Acidosis

The term *renal tubular acidosis* is used to describe a group of disorders that affect the ability of the renal tubules to secrete hydrogen ions or retain bicarbonate ions. These disorders can affect proximal or distal tubular function. The RTA syndromes are associated with the finding of hyperchloremic acidosis, without significant retention of anions such as phosphate or sulfate (as found in acidosis of glomerular impairment). Clinically, RTA should be suspected in patients with a non-anion gap (hyperchloremic) metabolic acidosis. Other causes of this biochemical abnormality include diarrheal states, dilutional acidosis, hyperalimentation, posthypocapnia, and addition of acidifying

salts. A urine anion gap (urine $Na^+ + K^+ - Cl^-$) is positive in RTA, whereas it is negative in other causes of hyperchloremic acidosis.

Type 4 RTA is characterized by a failure of hydrogen and potassium ion secretion in the collecting duct caused by aldosterone deficiency or resistance. This defect is most commonly associated with diabetes and tubulointerstitial disease, though it also has been well-described in hypertensive nephrosclerosis, systemic lupus erythematosus, and AIDS. Type 4 RTA is often observed in the context of a mild to moderate decrease in the glomerular filtration rate. The serum potassium level is high (5.5 to 6.5 mEq/L), causing decreased proximal tubule ammonium ion production, leading ultimately to a urine pH typically less than 5.5.⁷

Discussion of the Case Patient

We propose that the case patient had a persistent hyperkalemic, hyperchloremic non-anion gap acidosis (consistent with type 4 RTA) caused by spironolactone. We propose that this continued acidosis during both hospitalizations, after resolution of diarrhea and correction of renal function, suggests a prolonged action of spironolactone on the aldosterone pathway in this patient. Though not available, a urine anion gap calculation would have been helpful in confirming our hypothesis. The abnormalities continued, despite the patient reporting no spironolactone use during the 18 days preceding her second admission to the hospital. Canrenone, the chief active metabolite of spironolactone, has a half-life of 18 hours, and any effect from spironolactone lasting beyond 5 days was previously unknown.⁸

CONCLUSION

This case illustrates the need to exercise caution when initiating spironolactone treatment in elderly patients. Of particular concern is the use of this medication in patients with preexisting renal insufficiency or in those prone to hyperkalemia and dehydration. Metabolic status should be closely monitored in all elderly patients receiving treatment with spironolactone. **HP**

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