Case Report

Hyperchloremic Metabolic Acidosis Secondary to Spironolactone

B. Ruddock, C.D. Bayliff and D.G. McCormack

INTRODUCTION

Spironolactone is an aldosterone antagonist which is indicated for therapeutic management of several disease states including essential hypertension, hypokalemia, primary hyperaldosteronism, edema associated with congestive heart failure which has been unresponsive to other agents, and ascites associated with cirrhosis.[1,2] For patients with liver disease accompanied by hyperaldosteronism, aldosterone antagonists such as spironolactone are useful diuretics.[2,3] Generally, therapy is well tolerated; however, serious side effects may occur. We report a case of a less frequently encountered problem, hyperchloremic metabolic acidosis as a result of spironolactone therapy.

CASE

A 71 year-old male presented to the emergency department complaining of increasing shortness of breath for several days. He had experienced an occasional cough with sputum for the last few weeks, as well as normal-coloured, non-bloody diarrhea for one week. Two days prior to admission, the patient claimed to have vomited several times.

The patient's past medical history was extensive and included cirrhosis of the liver with ascites and hepatomegaly, cancer of the prostate treated with orchidectomy, Type II diabetes mellitus, chronic obstructive pulmonary disease, peptic ulcer disease, and hypertension. He had a 75 pack-year smoking history and admitted to drinking up to 24 beers daily for several years, until about five years previous, after which he drank occasionally. Review of systems was remarkable for the presence of chronic pedal edema, and orthopnea for one week.

The patient did not report any known drug allergies. His medications on admission included ranitidine 150 mg po bid, spironolactone 25 mg po bid, glyburide 10 mg po bid, salbutamol 200 mcg inhaled qid, lorazepam 1 mg po tid prn, temazepam 15 mg po qhs prn, loperamide 2 mg po qid prn, hydrocortisone cream 1% prn, and acetaminophen 325 mg po q6h prn.

On examination, the patient was in moderate respiratory distress sitting upright and was using accessory muscles of respiration. His blood pressure was 140/70 mmHg, heart rate 100 beats per minute and regular, respiratory rate 26 per minute, and he was afebrile. He was alert and oriented. Clubbing was present and chest examination revealed absence of breath sounds, dullness to percussion with decreased tactile fremitus over the right hemithorax, as well as decreased breath sounds over the left hemithorax. Remarkable cardiovascular findings included bilateral pitting edema to the midshins, and a jugular venous pressure 3 cm above the sternal angle. Other notable findings related to his liver disease were a positive Dupuytren's contracture, palmar erythema, spider nevi, and gynecomastia. Rectal exam revealed dark stool positive for occult blood.

Abnormal serum biochemistries were: chloride 118 mmol/L, bicarbonate 14 mmol/L, creatinine 153 µmol/L, BUN 21.2 mmol/L, WBC 11.6 x 10^9/L, hemoglobin 111 g/L, albumin 18 g/L, phosphate 1.85 mmol/L, and lactate dehydrogenase 237 U/L. Estimated creatinine clearance was 45 mL/min, anion gap was 11 and blood gases were: P_aO_2 65 mmHg, pH 7.25, P_aCO_2 35 mmHg, and HCO_3^- 13 mmol/L. Chest X-ray revealed a large right pleural effusion.

The patient was prescribed the following medications on admission to hospital: ranitidine 150 mg po bid, spironolactone 25 mg po bid, thiamine 100 mg IV daily for three days, and methylcellulose eye drops. Salbutamol 200 mcg inhaled qid and cotrimoxazole double strength tablets 1 po bid were started subsequently. A chest tube was inserted to drain the pleural effusion, which was determined to be a transudate of ascitic fluid leaking through a defect in the right hemidiaphragm. After one week in the hospital, serum potassium had risen to 7.5

B. Ruddock, BScPhm, is a Pharmacist, Pharmacy Services, Victoria Hospital, London, Ontario.

C.D. Bayliff, PharmD, FCSHP, is the Clinical Coordinator, Pharmacy Services, Victoria Hospital.

D.G. McCormack, MD, FRCP(C), is a Respirology Consultant, Medicine, Victoria Hospital.

Address correspondence to: Brent Ruddock, BScPhm, Pharmacy Services, Victoria Hospital, 375 South Street, London, Ontario, N6A 4G5.

mmol/L, serum bicarbonate had dropped to 13 mmol/L and serum chloride was 107 mmol/L. Arterial blood gases at the time were: P_aO_2 71 mmHg, pH 7.10, P_aCO_2 34 mmHg, and HCO_3^- 10 mmol/L, with an anion gap of 19.

The patient's hospital stay was prolonged and complicated by continued high output pleural/peritoneal fluid through his chest tube and he died several weeks later. During his prolonged course, there was no recurrence of his acid-base disorder.

DISCUSSION

Spironolactone and its active metabolites act at the distal convoluted tubule of the nephron where they compete with aldosterone. Because aldosterone increases potassium and hydrogen ion excretion, one might expect that hyperkalemia and metabolic acidosis would be frequent findings in patients taking spironolactone; however, this is not the case. In most individuals, electrolyte abnormalities are rarely seen, but in patients with cirrhosis, these changes seem to occur more often. This may be partly because cirrhotic patients are prone to low serum bicarbonate levels as a result of associated problems such as respiratory alkalosis, alcoholic diarrhea, or renal acidification defects.[3] It has been postulated that high potassium levels associated with spironolactone use may interfere with hydrogen ion excretion, thereby worsening metabolic acidosis.[3,4]

Gabow et al[3] reported six patients with alcoholic cirrhosis who developed hyperchloremic metabolic acidosis during spironolactone therapy. Spironolactone dosage ranged from 100 to 200 mg per day and the duration of drug therapy from one to seven weeks. Serum bicarbonate levels decreased from 18.2 ± 4.5 mEq/L to 10.9 ± 3.2 mEq/L during therapy, and increased to 18.1 ± 3.5 mEq/L upon withdrawal of the drug. Increased serum potassium also occurred during treatment, rising from 3.7 ± 0.5 mEq/L to 5.0 ± 0.8 mEq/L.

Feinfeld et al[4] reported a case of a 64 year-old man who developed hyperkalemia and hyperchloremic acidosis while receiving spironolactone 300 mg/day for treatment of ascites. Laboratory values were: potassium 9.0 mEq/L, chloride 111 mEq/L, carbon dioxide 8 mEq/L and a normal anion gap. Unfortunately, the patient's death prevented studies to confirm that spironolactone was the cause of the abnormalities, but other explanations were ruled out.

Campra et al[5] studied the effects of high dose spironolactone in patients with chronic liver disease and relatively refractory ascites. Doses ranged from 300 to 600 mg daily for 9 to 41 days. Three instances of transient hyperkalemia were noted, with potassium levels of 5.5 mEq/L, 5.6 mEq/L and 7.5 mEq/L.However, it was later established that the patient with a level of 7.5 mEq/L had been using a potassium chloride salt substitute during spironolactone therapy. Serum bicarbonate fell an average of 7 mEq/L and hydrogen ion excretion decreased initially, leading to mild hyperchloremic acidosis.

In our patient, spironolactone was determined to be the primary cause of the electrolyte disturbance; however, other complicating factors probably existed. For instance, on the day prior to the peak potassium concentration, the patient was started on cotrimoxazole which could have contributed to the increase in potassium.[6] This cannot; however, explain the accompanying metabolic acidosis. Some degree of lactic acidosis may have contributed to the low pH, as the anion gap was raised at 19 when it should be normal in metabolic acidosis solely secondary to spironolactone. The patient had also complained of diarrhea for the week prior to admission. As the diarrhea resolved in the first week of hospitalization, it was ruled out as the cause for the fall in serum bicarbonate. Non-compliance with spironolactone therapy at home may have been an issue in this case, as hyperkalemia did not develop until the patient was admitted to hospital. Accumulation of the active metabolites of spironolactone may have also been partly responsible for the observed abnormalities, as it has been shown that half-lives for these compounds are longer in cirrhotic patients.[7]

Even though there seem to be a number of confounding factors, discontinuation of spironolactone with resolution of biochemical abnormalities would suggest that it was chiefly responsible for the changes seen.

In conclusion, while spironolactone may be considered the diuretic of choice in cirrhotic patients with ascites, pharmacists and other health care professionals should be aware of the potential adverse effects on serum biochemistries and should monitor serum electrolytes carefully.

ADDENDUM

Since reporting this case, another instance of hyperchloremic metabolic acidosis secondary to spironolactone has been observed at our institution. An 80 year-old man with a history of alcohol abuse and possible alcoholic cirrhosis was admitted to the hospital with the following biochemistries: K^+ 6.8 mmol/L, Cl- 122 mmol/L, P_aO_2 104 mmHg, pH 7.19, P_aCO_2 24 mmHg, HCO_3^- 9 mmol/L and an anion gap of 11. His medications on admission included digoxin, enalapril, furosemide, potassium chloride, spironolactone, ranitidine, levothyroxine, temazepam, nitroglycerin, and Percodan®. Upon discontinuation of spironolactone, there was rapid improvement of biochemical abnormalities. The patient was discharged with instructions not to resume spironolactone.

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