

A Reversible Syndrome of Acute Renal Failure Associated with Renin-Angiotensin Inhibitor Drugs

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Abstract

Background and Aims: Previous studies indicate that angiotensin converting enzyme inhibitors (ACEI) cause acute renal failure (ARF) in patients with diabetes, hypertension, and congestive heart failure. Volume depletion is a determining factor for ACEI-induced ARF. This study presents a syndrome of reversible ARF accompanied by hyperkalemia, metabolic acidosis, and anemia associated with ACEI and angiotensin receptor blocker (ARB).

Methods: Data were collected from a total of 12 patients; 11 were admitted to the hospitals and 1 as an outpatient. Six patients had uncontrolled diabetes. Four of these patients also had hypertension. Eight patients (67 percent) received lisinopril; 4 (33 percent) received ARB. Diuretics were the commonest accompaniment. They showed moderate to severe azotemia. Estimated glomerular filtration rate (eGFR) ranged from 9.3 to 32.2 ml/min with an average eGFR of 14.1 ml/min. Six patients (50 percent) had moderate to severe hyperkalemia. All but 2 patients had metabolic acidosis, and 6 patients (50 percent) were anemic. ACEI or ARB and diuretics were discontinued in all patients, and all hospitalized patients were treated with normal saline or bicarbonate infusion, erythropoietin, and 9-alpha fluodrohydrocortisone, as required.

Results: Azotemia reversed and renal function improved to normal or near normal in 8 patients (67 percent). One of these patients required one-time hemodialysis. Renal function returned to baseline or better in 3 patients with preexisting renal insufficiency. Renal function improved in 1. All hyperkalemic patients became normokalemic, and all but 1 recovered from metabolic acidosis. Anemia also improved.

Conclusions: This novel observation substantiates our previous observation and further reiterates that ACEI/ARB causes a syndrome of reversible azotemia, hyperkalemia, metabolic acidosis, and anemia. Discontinuation of ACEI/ARB and diuretics—and treatment with a combination of bicarbonate infusion, 9-alpha fluodrohydrocortisone (Florinef®), and exogenous erythropoietin—hasten recovery from this syndrome. Continuation of a diuretic but without ACEI/ARB doesn't hinder renal function recovery.

Keywords: Acute Renal Failure, ACEI/ARB, Hyperkalemia, Metabolic Acidosis, 9-alpha Fluodrohydrocortisone, Erythropoietin

Introduction

Azotemia is a synonym for acute renal failure (ARF) or chronic renal failure (CRF) in this study. Acute renal failure or progression of CRF associated with use of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blocker (ARB) is increasingly observed. ARF, which is commonly

accompanied by metabolic acidosis, hyperkalemia, and anemia associated with the use of ACEI or ARB,

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constitutes a complex or a new syndrome. The most common underlying condition associated with this syndrome is uncontrolled diabetes. Other risk factors for this syndrome are diuretic therapy, elderly subjects, congestive heart failure (CHF) treated with high dose diuretic therapy, tube feeding with osmotic diuresis, chronic diarrhea, and vomiting with loss of fluid. The fundamental mechanisms of ARF are volume depletion and low blood pressure. We have reported that ARF developed in 1 of 41 patients (2.4 percent) who received ACEI alone, whereas ARF developed in 11 of 33 patients (33 percent) in those who received a combination of an ACEI and a diuretic. Renal function recovered upon discontinuance of ACEI and diuretics. Recovery was faster with normal saline infusion (1).

There is a prevalent belief that ACEI/ARB is renoprotective in diabetes from the result of several clinical trials (2-4). A recent study contradicts this popular belief. This study describes that ACEI use does not appear to reduce the long-term risk of end stage renal disease (ESRD) in diabetes. In fact, data from this study suggest that ACEI might actually increase this risk, which may possibly contribute to continued increasing incidence of ESRD owing to diabetes (5). The purpose of this communication is to reemphasize the risk of ARF associated with the use of ACEI/ARB, requiring hospitalization and increasing cost of healthcare. To that effect, several patients are presented to demonstrate the syndrome associated with ACEI/ARB.

Materials and Methods

This study has been approved by the Institutional Review Board of Flagler Hospital, St. Augustine, Florida. Estimated glomerular filtration rate (eGFR) was calculated from the modification of diet in renal disease equation as recommended by the National Kidney Foundation (6).

Patient Examples

Patient #1:

A 51-year-old white male was brought into the emergency room of a local hospital in an unresponsive state on December 3, 2006, and admitted into the Intensive Care Unit (ICU). He has had chronic back pain for which a morphine pump was implanted in his back. He had slurred speech and was breathing at a rate of 6 to 8 per min. His breathing and verbal response improved after a dose of intravenous naloxone. After he was awake, he gave a history of hypertension, diabetes, anxiety, and depression. His medication consisted of hydrochlorothiazide 25 mg p.o. daily, lisinopril 40 mg p.o. twice daily, promethazine 25 mg p.o. every 8h as required, gabapentin 400 mg p.o. 3 times daily, acetaminophen 325 mg as required, gemfibrozil (Lopid®) 600 mg p.o. twice daily, methocarbamol 500 mg p.o. 2 tablets 3 times daily, metformin 500 mg p.o. twice daily, morphine sulfate 60 mg p.o. 3 times daily, morphine sulfate 30 mg p.o. 3 times daily, nifedipine 30 mg p.o. twice daily, ezetimibe (Zetia®) 10 mg once daily, and fluoxetine hydrochloride (Prozac®) 20 mg p.o. once daily. Laboratory studies in the emergency room showed arterial blood gas pH 7.16, P_{CO_2} 48.2 mmHg, P_{O_2} 128.7 mm Hg after ventilation, HCO_3^- 17.1 mmol/L with a base excess of -11 mmol/L, sodium 127 mmol/L, potassium 6.1 mmol/L, chloride 91 mmol/L, CO_2 22 mmol/L, glucose 290 mg/dL, BUN 71 mg/dL, serum creatinine 6.3 mg/dL, hemoglobin 10.9 g/dL, hematocrit 32.2 percent, normochromic, normocytic anemia. His blood pressure was in the range of 80-90 mmHg systolic. An ultrasound of kidneys showed normal right kidney, left kidney hydronephrosis due to impacted calculi. All medications were discontinued. He was treated with dopamine and norepinephrine drip as well as methylprednisolone for low blood pressure. He also received infusion of normal saline with 2 ampoules of sodium bicarbonate per liter bag at a

rate of 60 ml/h. A Quinton catheter was placed, and he received 1 hemodialysis treatment for 4 hours. One unit of packed red blood cells was transfused during hemodialysis. Next day, he became alert and complained of severe pain in right foot. He has had previous surgery in right foot. Gout was ruled out as his uric acid was 5.1 mg/dL. An arterial blood gas on December 4, 2006, revealed normal values. Serum chemistry showed sodium 137 mmol/L, potassium 4.1 mmol/L, chloride 98 mmol/L, Co_2 32 mmol/L, glucose 135 mg/dL, BUN 34 mg/dL, serum creatinine 1.6 mg/dL, total protein 7.2 g/dL, albumin 3.3 g/dL, calcium 8.7 mg/dL, and phosphorus 2.4 mg/dL. Since no additional hemodialysis was required, Quinton catheter removed. One dose of 40 mg furosemide was intravenously given. He produced 2700 ml urine in 24 hours. Four days later, BUN, serum creatinine, electrolytes, and calcium were all normal. Estimated GFR was 75 ml/min ($n \geq 60$ ml/min). He became fully alert and oriented. His blood pressure was within normal range. He was transferred from the ICU to rehabilitation but lost for further follow up.

Comment:

The patient was brought into the emergency room of a hospital in an unresponsive state with markedly decreased respiratory rate both of which were due to morphine. He woke up after an intravenous dose of naloxone. He was found to have developed renal failure acute vs. chronic, hyponatremia, hyperkalemia, metabolic acidosis (arterial pH 7.16, HCO_3 17.1 mmol/L). High Pco_2 indicates mixed respiratory acidosis and metabolic acidosis in this setting. Respiratory acidosis was due to morphine. Since no previous data on renal function was available, renal failure was considered acute. Hydrochlorothiazide (HCTZ) caused hyponatremia, but HCTZ in and of itself doesn't cause renal failure. Further renal failure in association with hyperkalemia, metabolic acidosis, and anemia was certainly due to lisinopril.

Diuretics cause metabolic alkalosis and hypokalemia. Therefore, HCTZ attenuated to an extent the severity of metabolic acidosis and hyperkalemia. On the other hand, metformin aggravated metabolic acidosis to an extent. Prozac occasionally causes hyponatremia. Gemfibrozil and zetia together occasionally causes myopathy, myoglobinuria and acute renal failure but is almost invariably associated with hyperuricemia. His serum uric acid was normal. Methocarbamol is a muscle relaxant and has no known effect on renal function, electrolytes or acid-base status. A characteristic feature of ACE inhibitors is very low blood pressure (BP), which is often aggravated by diuretic therapy (7). This patient had very low BP, requiring vasopressor therapy and steroids to increase BP. Such a low BP decreases renal perfusion, leading to ARF. For that reason, normal saline or bicarbonate infusion rapidly reverses ACEI/ARB-induced ARF by increasing BP and, consequently, renal perfusion. His BP increased in parallel with improvement in renal function.

Patient #2:

A 51-year-old white female was admitted into the ICU of a local hospital through emergency room on May 20, 2006, with the complaints of increased shortness of breath and anuria (no urine output) for 24 hours. Her renal function was normal in the past. Her medication consisted of clopidogrel (Plavix®), simvastatin 40 mg p.o. daily, isosorbide 30 mg p.o. twice daily, and lisinopril 40 mg p.o. daily. An arterial blood gas showed pH 7.27, Hco_3 17.4 mmol/L. Chemistry showed BUN 97 mg/dL, serum creatinine 4.0 mg/dL, eGFR 12.5 ml/min, sodium 137 mmol/L, potassium 4.8 mmol/L, and Co_2 16 mmol/L. Lisinopril was discontinued. She was treated with furosemide infusion (furosemide 240 mg/500 ml one-half normal saline) at 21 ml/h and bicarbonate infusion (2 ampoules of sodium bicarbonate in a liter of 5 percent dextrose in water) at 50 ml/h. Her urine output promptly increased and reached several liters

daily. Her renal function started to improve. Four days later on May 24, 2006, a chemistry showed BUN 27 mg/dL, serum creatinine 1.0 mg/dL, with eGFR of 62 ml/min ($n > 60$ ml/min), sodium 143 mmol/L, potassium 4.1 mmol/L, and Co_2 38 mmol/L. Furosemide and bicarbonate infusion were discontinued. On June 2, 2006, her serum chemistry was normal. She was discharged to a nursing home.

Comment: This patient was not taking other medicine than lisinopril that will cause ARF. Therefore, lisinopril is the only drug that can be incriminated to cause ARF. Furthermore, ACEI, especially lisinopril, can lead to oliguria or anuria as in this patient. Furosemide infusion promptly increased her urine output by increasing renal perfusion pressure. Prompt reversal of ARF to normal renal function after withdrawal of lisinopril is a compelling evidence that lisinopril caused ARF in this patient.

Patient #3:

A 46-year-old African-American female, full-time employee, was admitted to a hospital on December 30, 2001, with the complaint of nausea, vomiting, dizziness, and low urine output. She was found to have azotemia. On September 27, 2001, her primary care physician prescribed a combination of lisinopril and hydrochlorothiazide for control of hypertension. Laboratory on July 10, 2001, was normal. On December 30, 2001, at the emergency room her laboratory showed BUN 67 mg/dL, serum creatinine 5.6 mg/dL, sodium 130 mmol/L, potassium 4.5 mmol/L, chloride 97 mmol/L, Co_2 19 mmol/L, glucose 103 mg/dL, hemoglobin 10.9 g/dL. Lisinopril and hydrochlorothiazide were discontinued, and she was treated with normal saline infusion at 60 ml/h. Two days later, on January 1, 2002, laboratory showed BUN 32 mg/dL, serum creatinine 1.5 mg/dL, normal electrolytes, Co_2 19 mmol/L, and hemoglobin 10.5 g/dL. Normal saline infusion was discontinued. She was discharged from the hospital. At a follow-up office visit on February 18, 2002, her laboratory values

were all normal. Her hemoglobin increased to 12.7 g/dL. She did not receive exogenous erythropoietin.

Comment: This patient had documented normal renal function 5 months prior to development of ARF. She was not taking any other medicine except HCTZ and lisinopril, which caused her ARF. HCTZ commonly causes hyponatremia (Na^+ 130 mmol/L) in this patient as well as in other patients. Serum K is normal because of HCTZ. Reversal of ARF to normal renal function after withdrawal of lisinopril indicates that ARF was caused by lisinopril. Mild volume depletion caused by HCTZ adds to low BP produced by ACEI(7), resulting in rapidly decreased renal perfusion and rapid onset of ARF. The rapid recovery of renal function assisted by fluid therapy is associated with increase in BP and, hence, increase in renal perfusion.

Patient #4:

A 59-year-old African-American male with a long history of diabetes mellitus was admitted to a local hospital on August 18, 2005, with a diagnosis of ARF. It was not evident if he was taking insulin. He was taking lisinopril 20 mg p.o. daily. His admission laboratory showed glucose 402 mg/dL, BUN 76 mg/dL, serum creatinine 7.4 mg/dL, sodium 126 mmol/L, potassium 5.9 mmol/L, and Co_2 15 mmol/L. Lisinopril was discontinued. One day later, laboratory showed glucose (fasting) 274 mg/dL, BUN 80 mg/dL, serum creatinine 8.2 mg/dL, sodium 127 mmol/L, potassium 5.0 mmol/L, Co_2 17 mmol/L. An arterial blood gas analysis showed pH 7.31 with base excess -7.7 mmol/L. He was treated with regular insulin on a sliding scale, kayexalate, and infusion of normal saline with 3 ampoules of sodium bicarbonate per liter bag at a rate of 60 ml/h. Three days later, his laboratory values were BUN 22 mg/dL, serum creatinine 0.8 mg/dL, sodium 139 mmol/L, potassium 4.2 mmol/L, and Co_2 32 mmol/L. His glucose control improved. Bicarbonate infusion was discontinued. He was discharged from

the hospital. At a follow-up visit, he was doing fine.

Comment: This patient was taking only medicine that was lisinopril. He showed uncontrolled hyperglycemia, which almost always sets up the volume changes for lisinopril to cause ARF. The fact is that control of glucose with insulin accompanied by discontinuation of lisinopril and bicarbonate infusion resulting in complete reversal of ARF is a strong clue to lisinopril-induced ARF.

Patient #5:

A 75-year-old white male with a long history of diabetes and hypertension was admitted into the ICU of a local hospital on March 27, 2002, for gastrointestinal bleeding. Medication consisted of lisinopril 10 mg p.o. twice daily, furosemide 40 mg p.o. daily, and insulin as required. He was previously admitted to the same hospital for renal insufficiency. His medication then included lisinopril 5 mg p.o. daily and furosemide 20 mg p.o. daily. His BUN was 33 mg/dL and serum creatinine was 1.9 mg/dL. Lisinopril was discontinued. Primary care physician restarted him on lisinopril 10 mg p.o. twice daily. His admission laboratory showed BUN 128 mg/dL, serum creatinine 3.9 mg/dL, sodium 139 mmol/L, potassium 7.4 mmol/L, Co_2 19 mmol/L, glucose 341 mg/dL, hemoglobin 8.4 g/dL. Lisinopril and furosemide were discontinued. Endoscopy showed bleeding duodenal ulcer. He was treated with packed cell transfusion, normal saline infusion, regular insulin on a sliding scale, kayexalate, and 9-alpha fluodrohydrocortisone (Florinef®) for hyperkalemia. Three days later, on March 30, laboratory values were much improved: BUN 68 mg/dL, serum creatinine 1.8 mg/dL, sodium 144 mmol/L, potassium 4.3 mmol/L, hemoglobin 9.3 g/dL, and hemacrit 29.0 percent. Glucose control also improved. He was discharged from the hospital with the advice to follow up with a nephrologist.

Comment: This patient had chronic renal failure. Lisinopril caused deterioration of renal function, which improved every time upon discontinuation

of lisinopril. Severe hyperkalemia (Serum K 7.4 mmol/L), despite furosemide, which causes hypokalemia, is a strong evidence of lisinopril's adverse effect.

Patient #6:

A 47-year-old white male was admitted to a hospital on June 23, 2006, for groshong catheter (tunneled catheter with a cap for intravenous therapy) malfunction. In the hospital, he was noted to have ARF. His medication consisted of lisinopril 5 mg p.o. daily, carvedilol 12.5 mg p.o. daily, furosemide 20 mg p.o. daily, and Lipitor® 20 mg p.o. daily. On June 18, 2006, prior to hospital admission, his renal function was normal. At the hospital on June 23, his laboratory showed BUN 52 mg/dL, serum creatinine 2.2 mg/dL, sodium 132 mmol/L, potassium 4.6 mmol/L, Co_2 19 mmol/L, and glucose 237 mg/dL. Lisinopril and furosemide were discontinued. He was treated with normal saline infusion at 60 ml/h x 48h. Two days later, his renal function and electrolytes were normal. Glucose was also decreased to 157 mg/dL.

Comment: This patient, like Patient #3, was taking a diuretic and lisinopril. Again, his renal function returned to normal upon discontinuation of lisinopril and furosemide and fluid therapy, which makes a strong argument that volume depletion is an important determining factor for ACEI-induced ARF.

Patient #7:

A 67-year-old African-American female was admitted to a local hospital on January 29, 2002, for severe shortness of breath and weakness. She gave a history of diabetes, hypertension, chronic obstructive pulmonary disease, and CRF. Her medication consisted of synthroid 50 mcg p.o. daily, Actos® 45 mg p.o. daily, Novolin® 70/30 30 units subcutaneously in the morning and 25 units in the evening, Neurotin® 600 mg p.o. twice daily, irbesartan (Avapro®) 150 mg p.o. twice daily, furosemide 80 mg

p.o. in the morning and 40 mg p.o. in the evening, metolazone 2.5 mg p.o. daily, Vioxx® 25 mg p.o. daily, Premarin® 0.625 mg p.o. daily, and albuterol inhalation as needed. As of January 5, 2001, laboratory showed BUN 35 mg/dL, serum creatinine 2.6 mg/dL, and glucose 137 mg/dL. One year later at the time of hospital admission, dramatic changes were noted in the laboratory studies: BUN 86 mg/dL, serum creatinine 5.8 mg/dL, sodium 134 mmol/L, potassium 3.3 mmol/L, chloride 89 mmol/L, Co_2 35 mmol/L, and random glucose 800 mg/dL. Irbesartan, furosemide, and metolazone were discontinued. Four days later, her BUN and serum creatinine decreased to 52 mg/dL and 4.2 mg/dL, respectively. Electrolytes and glucose levels were normal. On February 12, 2002, irbesartan, furosemide, and metolazone were restarted. Nine days later, renal function deteriorated as evidenced by elevation of BUN and serum creatinine to 69 mg/dL and 4.4 mg/dL, respectively. Seven days later, irbesartan, furosemide, and metolazone were once again discontinued. She did not take irbesartan again, although she takes furosemide as required to keep her swelling off. Four years later, February 6, 2006, her renal function was at baseline level: BUN 30 mg/dL, serum creatinine 3.1 mg/dL. However, her glucose control varied.

Comment:

This patient was taking Vioxx (nonsteroidal anti-inflammatory drug), which can cause ARF. She continued to take Vioxx, but renal function improved upon withdrawal of irbesartan. Reinstitution of irbesartan resulting in decline of renal function is almost *sine qua non* that ACEI/ARB causes reversible ARF.

Patient #8:

A 70-year-old white male was admitted to a local hospital on April 26, 2003, not feeling well. Past medical history included blackout spells, chest pain and right upper pneumonectomy in 1992, and removal of 4/5th stomach in 1969. Blood pressure was in the

range of 93/57 mmHg sitting. Medication consisted of irbesartan, nitroglycerine furosemide, minoxidil, and potassium supplements. His admission laboratory showed BUN 58 mg/dL, serum creatinine 3.1 mg/dL, sodium 132 mmol/L, potassium 5.6 mmol/L, chloride 99 mmol/L, Co_2 20 mmol/L, glucose 252 mg/dL, hemoglobin 12.3 g/dL. Two days later, his BUN increased to 71 mg/dL with unchanged serum creatinine. All medications, except nitroglycerine, were discontinued; 5 percent dextrose in half normal saline was infused at 60 ml/h for 48 hours. On May 2, 2003, he was discharged from the hospital with the advice to follow up in a nephrologist's office. A serum chemistry on May 28, 2003, showed BUN 21 mg/dL, serum creatinine 1.3 mg/dL, and normal electrolytes. Glucose was 109 mg/dL and hemoglobin 11.1 g/dL. In an office visit on June 3, 2003, he felt well and blood pressures were normal.

Comment:

In this patient, serum potassium was high despite furosemide intake. It could have been higher if he was not taking furosemide. His renal function returned to near-normal level upon discontinuation of irbesartan and furosemide and fluid therapy. Furosemide, like HCTZ, can increase blood glucose, mimicking diabetes. In fact, many of these patients are labeled as Type 2 diabetes and placed on oral antidiabetic agents. Fluid therapy with glucose in the solution decreased glucose to normal (109 mg/dL), indicating volume depletion is an important cause of hyperglycemia.

Patient #9:

An 88-year-old African-American female was admitted to a local hospital on November 21, 2005, with history of nausea, vomiting, extreme weakness, and dizziness. She had diabetes. Poor skin turgor and low blood pressure were noted. On November 11, 2005, a serum chemistry showed BUN 31 mg/dL, serum creatinine 1.5 mg/dL, normal electrolytes, and

Co₂. Glucose was 172 mg/dL. Medication consisted of lisinopril 20 mg p.o. daily, furosemide 20 mg p.o. daily, simvastatin 40 mg p.o. daily, Amaryl® 4 mg p.o. daily. On the day of admission, serum chemistry showed BUN 78 mg/dL, serum creatinine 2.9 mg/dL, sodium 137 mmol/L, potassium 6.5 mmol/L, Co₂ 24 mmol/L, and glucose 208 mg/dL. Lisinopril and furosemide were discontinued, and she was treated with normal saline infusion at 50 ml/h x 3 days. Regular insulin was administered on a sliding scale. Six days later on November 27, her laboratory returned to better than baseline on November 11, 2005.

Comment:

Same as other patients already stated.

Patient #10:

A 90-year-old white female was admitted to a local hospital for ARF and urinary tract infection. Medication at the time of admission consisted of Levaquin®, Flagyl®, telmisartan (Micardis®), spironolactone, furosemide, and losartan (Cozaar®). Her laboratory at the time of admission included BUN 80 mg/dL, serum creatinine 2.6 mg/dL, sodium 137 mmol/L, potassium 5.6 mmol/L, Co₂ 15 mmol/L, hemoglobin 13.4 g/dL. Furosemide was discontinued. She was treated with normal saline infusion and kayexalate. A day later, telmisartan was discontinued. Seven days later, her laboratory showed BUN 46 mg/dL, serum creatinine 1.9 mg/dL, normal electrolytes, Co₂, and hemoglobin. Three days later, losartan was discontinued. Within 24 hours, laboratory showed further decrease of BUN and serum creatinine, normal electrolytes, Co₂, and hemoglobin.

Comment: This patient was taking 2 different ARBs: telmisartan and losartan. Seven days after discontinuation of telmisartan, renal function improved and more so after discontinuation of losartan, supporting that these drugs were causing the renal function to decrease.

Patient #11:

Here is an example of the most current patient whose renal function continues to improve with discontinuation of ACEI/ARB, but with continuation of a potent diuretic, such as bumetanide. A 66-year-old African-American male, admitted for shortness of breath from chronic obstructive pulmonary disease and swelling of legs, was seen in consultation by a local nephrologist for renal failure. Note that his kidney function is already reduced to chronic kidney disease (CKD) stage 3, and he is anemic (Table 1). Anemia is a common complication of ACEI/ARB, not recognized intentionally or unintentionally. Nephrologist's impression was renal failure due to high uric acid causing uric acid nephropathy. Uric acid was 6 mg/dL (n=3.4-7 mg/dL) on August 10, 2009. He recommended continue current therapy, including losartan, and considered addition of an ACE inhibitor. He didn't mention that ARF was due to losartan but permitted the patient to progress to severe renal failure. He told the patient that he would need dialysis soon. Patient refused dialysis.

The primary care physician cancelled this nephrology consultation and referred to me. Here are serial lab reports of this patient (Table 1).

This patient was followed by me from August 18, 2009. Furosemide and losartan were discontinued as of August 18. He was later on placed on bumetanide (Bumex) 1 mg orally daily, a potent diuretic, for edema of both legs. But renal function continued to improve despite use of bumetanide (Table 2).

His total kidney function plunged to 14 ml/min eGFR (normally >60 ml/min) on August 18.

Comment: After discontinuation of losartan but with continuation of a diuretic, his renal function continues to improve. eGFR increased to 45 ml/min, and hemoglobin increased to 13 g/dL. He feels very well and happy.

Progressive renal failure in this patient and all previous patients is a compelling evidence that ACEI/ARB make the patients a prey of dialysis.

This patient surely would have gone to dialysis if he was not transferred to my care.

Table 1. Initial Laboratory Results from a 66-year-old African-American Male treated with a combination of ARB, Losartan, and Bumetanide who developed Acute Renal Failure

Normal Range	August 2009 Dates	10 th	11 th	12 th	14 th	17 th	18 th
6 – 19	BUN (mg/dL)	21	21	20	21	34	37
0.8 – 1.5	Scr (mg/dL)	1.92	2.02	1.96	2.69	3.36	4.15
> 60	eGFR (ml/min)	37	35	37	25	20	15
3.5 – 5.0	Serum K (mmol/L)	4.2	4.0	3.9	4.0	3.9	3.7
24 – 34	Serum CO ₂ (mmol/L)	28	31	31	32	35	35
13.5 – 18	Hemoglobin (g/dL)	12.9	11.4	NA	11.9	11.5	NA

Scr, Serum Creatinine; **eGFR**, estimated Glomerular Filtration Rate; **K**, serum potassium; **NA**, not available.

Table 2. Laboratory Results from a 66-year-old African-American Male After Discontinuation of ARB, Losartan but continued with Bumetanide and showing Recovery from Acute Renal Failure

Normal Range	6 – 19	0.8 – 1.5	> 60	3.5 – 5.0	24 – 34	13.5 – 18	
Lab Panel No	BUN	Scr	eGFR (ml/	Serum K	Serum CO ₂	Hemoglobin	Uric
Losartan	(mg/dL)	(mg/dL)	min)	(mmol/L)	(mmol/L)	(g/dL)	Acid
19 Aug '09	44	4.51	16.9				
20 Aug '09	43	3.81	17				
21 Aug '09	38	3.04	22				
8 Sep '09	12	1.86	39	3.9	28	12.9	5.1
6 Oct '09	17	1.65	45	3.9	27	13.0	
3 Dec '09	15	1.30	59	4.1	29	13.9	5.8
17 Feb '10	14	1.44	52	4.0	29	12.9	

Scr, Serum Creatinine; **eGFR**, estimated Glomerular Filtration Rate; **K**, Serum potassium.

Patient #12—long-term follow up:

A 78-year-old African-American female was seen in office on December 21, 2004, with diagnosis of ARF secondary to lisinopril, uncontrolled hypertension, and CHF. Medication consisted of prazosin 2 mg daily, K-Lor 10 mEq twice daily, allopurinol 300 mg daily, furosemide 80 mg daily, diltiazem 300 mg daily. Lisinopril and hydrochlorothiazide were discontinued on December 15, 2004. In the office, her

blood pressure sitting was 120/70 mmHg. Allopurinol was reduced to 150 mg p.o. daily, furosemide reduced to 20 mg p.o. daily. Her serial BUN, serum creatinine, and creatinine clearance are presented in Figure 1. BUN and serum creatinine decreased to normal level and creatinine clearance or eGFR increased to normal level. Her hemoglobin and hematocrit increased to normal levels without administration of exogenous erythropoietin. The data are presented in Figure 2.

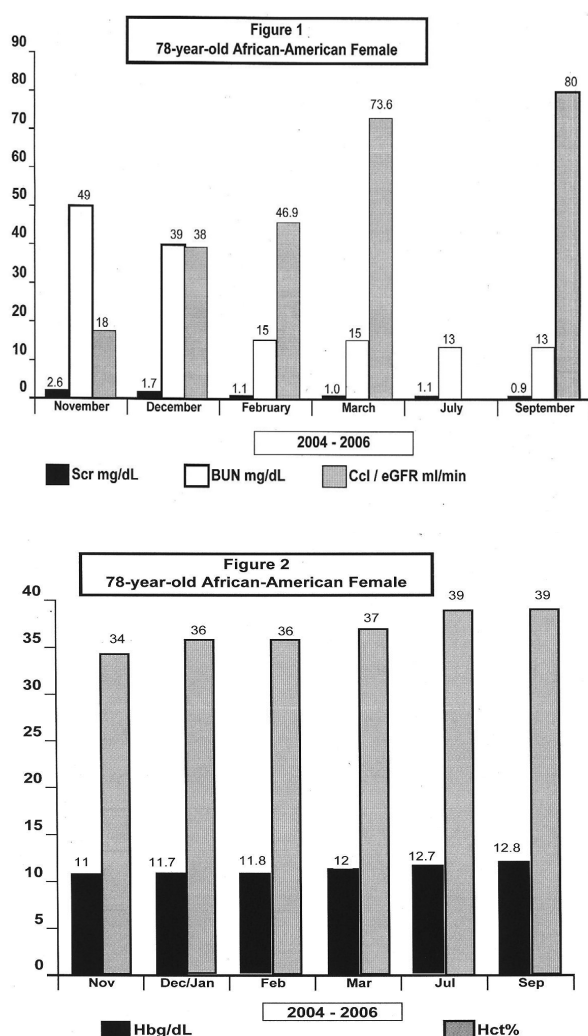


Figure 2. Shows serially hemoglobin (Hb) and hematocrit (Hct) levels over the same period as Figure 1. Hb and Hct progressively increased to normal levels in parallel with recovery of renal function to normal

Comment: Furosemide and losartan were discontinued. He received infusion of normal saline with potassium chloride for a brief period. Intravenous fluid was discontinued and bumetanide (Bumex®) 1 mg orally was started because of increased swelling of his legs.

Results

The youngest patient in this series was 46 years and the oldest one was 90 years. Mean age of the total 12 patients was 65.6 years. Six were males and 6 females. Six had diabetes (50 percent), 4 of them also had hypertension; 3 had hypertension but no diabetes, and 1 each had history of urinary tract infection and CHF. Eight patients (67 percent) received ACEI (lisinopril); 4 patients (33 percent) received ARB (losartan, irbesartan, telmisartan). Ten patients concomitantly received diuretic(s) (furosemide, hydrochlorothiazide, metolazone, bumetanide) (83 percent). The laboratory results before (pre), during (upon admission), and after discontinuance (post) of ACEI and ARB therapy in 1-10 patients can be found at a glance in Table 3. Wherever available pre-eGFR was normal or slightly reduced. During admission, BUN and serum creatinine were uniformly elevated, and eGFR or creatinine clearance (Ccr) were uniformly reduced. Initial eGFR/Ccr was less than 20 ml/min in 9 patients (82 percent). In a matter of a few days, after discontinuance of ACEI/ARB therapy and with fluid therapy, eGFR reached normal (>60 ml/min) in 5 of 10 patients (50 percent). Estimated GFR increased to near normal in 3 patients. In 2 patients, eGFR recovered to baseline. Fifty percent of the patients had hyperkalemia, and 75 percent of the patients had metabolic acidosis. Hyperkalemia and metabolic acidosis remitted after discontinuance of ACEI/ARB and with bicarbonate infusion. Seven patients (58 percent) had anemia, which improved with improvement of renal function and exogenous erythropoietin administration. In a long-term follow up (Patient #12), renal function returned to normal and has remained normal.

Table 3. Renal Function Parameters, Electrolytes, and Hemoglobin Before (pre), During (upon admission), and After Discontinuation (post)*

Patient	1	2	3	4	5	6	7	8	9	10
Age, Race, Gender	51 WM	51 WF	46 AAF	59 AAM	75 WM	47 WM	67 AAF	70 WM	88 AAF	90 WF
Diagnosis	Diabetes, Hypertension	CHF	Hypertension	Diabetes	Diabetes, Hypertension	Chrohn's disease, Diabetes	Diabetes, Hypertension, COPD	Hypertension	Diabetes	Urinary infection
ACEI, ARB, Diuretic	Lisinopril, HCTZ	Lisinopril	Lisinopril, HCTZ	Lisinopril	Lisinopril, Furosemide	Lisinopril, Furosemide	Irbesartan, Furosemide, Metolazone	Irbesartan, Furosemide	Lisinopril, Furosemide	Telmisartan, Losartan, Furosemide
BUN/Scr(mg/dL)	Pre	NA	11 / 0.8	NA	33 / 1.9	15 / 0.6	35 / 2.6	NA	31 / 1.5	NA
	During	71 / 6.3	99.3	76 / 7.4	36.9	153.4	23.6	71 / 3.1	42.1	80 / 2.6
	Post	10	14.1	9.8	16.0	32.2	9.3	21.2	19.6	18.3
		24 / 1.0	16 / 0.9	22 / 0.8	68 / 1.8	32 / 1.0	36 / 2.8	21 / 1.3	27 / 1.2	38 / 1.6
eGFR (ml/min)	83.7	118	86.6	127.2	39.2	85.1	21.6	58	54.5	32.1
Na / K (mmol/L)	pre	NA	140 / 3.5	NA	NA	NA	137 / 3.7	NA	141 / 4.1	NA
	During	127 / 6.1	130 / 4.5	126 / 5.9	139 / 7.4	132 / 4.6	134 / 3.3	128 / 5.6	137 / 6.5	137 / 5.6
	Post	137 / 3.7	134 / 3.7	140 / 3.8	144 / 4.3	132 / 3.5	136 / 4.9	138 / 4.9	136 / 4.3	141 / 4.1
Co ₂ (mmol/L)	Pre	NA	23	NA	NA	NA	30	NA	28	NA
	During	17.1	19	15	19	19	35	20	24	15
	Post	24	24	33	20	26	27	24	21	29
Hb (g/dL)	Pre	NA	11.9	NA	NA	13.7	NA	NA	NA	NA
	During	10.9	10.9	NA	8.4	10.6	NA	12.8	11.5	11.9
	Post	10.7	12.9	NA	9.3	NA	NA	11.1	10.3	11.6
Glucose (md/dL)	Pre	NA	110	NA	NA	NA	151	NA	172	NA
	During	290	103	402	341	237	800	252	208	NA
	Post	135	87	186	152	157	101	109	172	NA

Discussion

This novel study affirms that ACEI/ARB group of drugs causes reversible ARF. Further, the present study reveals that these drugs also cause hyperkalemia and metabolic acidosis in a majority of the patients. Discontinuation of these drugs and treatment with bicarbonate infusion and 9-alpha fluodrohydrocortisone (Florinef®) hasten recovery of renal function and cause reversal of hyperkalemia and metabolic acidosis. Exogenous erythropoietin accelerates correction of anemia in this syndrome. Bicarbonate infusion consists of half normal, normal saline, or 5 percent dextrose in water with 1 to 3 ampoules of sodium bicarbonate (44.5 mmol of sodium bicarbonate per ampoule). Bicarbonate content in the fluid depends on serum bicarbonate level and arterial pH. Preferred vehicle for bicarbonate infusion is 5 percent dextrose in water, if patient is not diabetic. Choice of half normal or normal saline depends on serum sodium level. The infusion rate is 50 to 60 ml/h.

By definition, all patients in this study developed ARF usually heralded by the elevation of serum creatinine ≥ 0.5 mg/dL from the baseline. Although no consensus exists on definition of ARF, it is reasonable to define ARF as ≤ 2 week increase in serum creatinine of 0.5 mg/dL for patients with baseline serum creatinine of < 2.5 mg/dL (8). Renal function can deteriorate soon after ACEI therapy is initiated, as in Patient #3, or in patients receiving chronic ACEI therapy, particularly in patients with CHF, as in Patient #11 and Patient #12. ARF can occur even if ACEI therapy has been uneventful for months or years (9-13). These previous observations are consistent with a current published report that reveals that long-term use of ACEI might actually increase the risk of ESRD (5). In our observation, duration of ACEI/ARB therapy was not known, except in Patient #3 who received ACEI for 3 months before she developed ARF, and in Patient #7 who received ARB

for a year before she developed ARF. Recurrence of renal function deterioration with reinstitution of ACEI/ARB, as in Patient #7, is strong evidence that these drugs are directly related to ARF.

Volume depletion from concomitant diuretic therapy, as in most of the patients, or from osmotic diuresis, as in uncontrolled diabetes (Patient #4) potentiates ACEI/ARB-induced ARF (1, 14). Very low BP caused by ACEI/ARB (7) is additive to volume depletion and decreased renal perfusion. Strong evidence for that is the fact that volume replacement in the form of normal saline or bicarbonate infusion hastens recovery from ARF. Bicarbonate infusion hastens recovery of eGFR faster than normal saline alone, if ARF is associated with metabolic acidosis, as shown in this study and our previous study (14). As long as renal perfusion pressure is adequate and volume depletion is not severe, ACEI is unlikely to cause ARF (1). However, because angiotensin II is necessary for maintenance of GFR during states of significant volume depletion and low blood pressure—such as uncontrolled diabetes, diuretic therapy, old age, chronic diarrhea, or vomiting—further suppression of angiotensin II with ACEI/ARB therapy can cause GFR to decline rapidly with consequent oliguric or anuric ARF (9). Patient #2 was anuric for 24 hours. Continuation of diuretic therapy does not prevent recovery of renal function, as in Patient #11.

Elderly subjects (> 65 years) are likely to develop this syndrome. Mean age of this cohort was 65.6 years. Metabolic acidosis and hyperkalemia are, at least in part, due to hyporeninemia and hypoaldosteronism associated with diabetes and are further aggravated by the use of ACEI/ARB. It has been generally accepted that acidosis increases plasma potassium concentration primarily mediated via a shift in potassium between intracellular and extracellular compartments (15). Hence, bicarbonate infusion and use of 9-alpha fluodrohydrocortisone (aldosterone analog) hasten reversal of hyperkalemia and

metabolic acidosis. Fluodrohydrocortisone (Florinef®) additionally promotes renal perfusion by the increase of blood pressure.

Acute renal failure in the intensive care settings is common and carries a high risk of mortality (16). There was no mortality observed in our study population mainly due to prompt initiation of bicarbonate infusion. Hemodialysis is indicated in severe ARF associated with moderate to severe metabolic acidosis and hyperkalemia (16). However, low dose continuous bicarbonate infusion at a rate 50-60 ml/h for several days appears to be an effective substitute for hemodialysis for ACEI/ARB-induced ARF in the ICU settings, as shown in our study.

There is no report of this syndrome in the literature, except some investigators have noted that, with use of ACEI/ARB, a profound fall in urinary protein only at the expense of an increase in serum potassium and greater fall in hematocrit (17). Moderate to severe hyperkalemia, as in Patients #1, #4, #5, and #9, is a distinct threat making physicians to admit these patients in a critical care unit with escalating cost of healthcare as reported by other authors (18). The risk of hyperkalemia is much higher in diabetes than other medical conditions due to preexistent hyporeninemia and hypoaldosteronism (19, 20). This risk is even higher, leading to life-threatening hyperkalemia, when ACEI is used in combination with spironolactone (21, 22). However, concomitant high dose diuretic(s) therapy, as in Patient #7 and Patient #11, helps to mitigate hyperkalemia and metabolic acidosis.

Among all the ACE inhibitors used, lisinopril has been found to be the most common ACEI associated with this syndrome. Eight of 12 patients in this study were treated with lisinopril. Lisinopril is also found as the most common ACEI in many patients with mild form of this syndrome who were not hospitalized and are not reported here.

Conflict of Interest

None declared.

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