**CLINICAL VIGNETTE**

# Severe Hyperkalemia Following Initiation of Low-Dose Lisinopril in an Elderly Nursing Home Patient

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***Case Presentation***

A 90-year-old female nursing home resident was seen for a routine follow up. Past medical history includes hypertension, chronic kidney disease, obesity, dyslipidemia, prediabetes, prior carotid artery stent placement, mild cognitive impairment, seizure disorder, hypothyroidism, GERD, chronic pain, recurrent falls, and wheelchair dependence. Elevated blood pressure was noted throughout her nursing home stay, and she was not currently on anti-hypertensive medications. Current medications include daily levothyroxine 60 mg, duloxetine 30 mg, famotidine 10 mg, aspirin 81 mg and tramadol 50 mg. She also receives levetiracetam 500 mg BID, acetaminophen 1000 mg TID, 50 mg q6h PRN, melatonin 3 mg QHS, lidocaine patch, polyethylene glycol power 17 gm, and docusate 100 mg BID. Vitals notable for a blood pressure of 159/89 mm Hg. Laboratories showed serum creatinine (Cr) 1.01 mg/dL (baseline 1.0-1.1 mg/dL; estimated glomerular filtration rate (GFR) 51), blood urea nitrogen (BUN) 26 mg/dL, and potassium 4.8 mg/dL.

The patient was started on daily lisinopril 10 mg for treatment of hypertension. Chemistries were repeated 14 days later and showed Cr 1.21 mg/dL and potassium 5.4 mg/dL. The decision was made to continue lisinopril and obtain a repeat, confirmatory potassium. The following day, the patient reported a productive cough, with associated wheezing. She was afebrile without tachycardia, hypotension, or hypoxia. Physical exam included non-toxic general appearance, mild expiratory wheezing, and crackles over left lung field. Chest x-ray showed a slight infiltrate in the left upper lobe. Testing for COVID-19 was negative. The patient was treated for pneumonia with cefpodoxime proxetil 200 mg BID and azithromycin 500 mg once followed by 250 mg daily for a 5-day antibiotic course. She also received benzonatate and albuterol nebulizer treatments as needed for symptom relief.

On the 4$^{th}$ day of the antibiotic course, repeat laboratories included: sodium 138 mg/dL, potassium 6.1 mg/dL, chloride 105 mg/dL, carbon dioxide 22 mg/dL, BUN 43 mg/dL, Cr 1.21 mg/dL. There was no mention of hemolysis in the laboratory report. Lisinopril was discontinued and the patient was treated with sodium zirconium cyclosilicate (10 mg TID for a total of 3 doses) in the nursing home. Repeat chemistry after zirconium treatment showed potassium 5.1 mg/dL and Cr 1.02 mg/dL. After clinical improvement from the pneumonia, the patient remained hypertensive and she was started on amlodipine 2.5 mg daily for further management of hypertension. Lisinopril has been permanently discontinued.

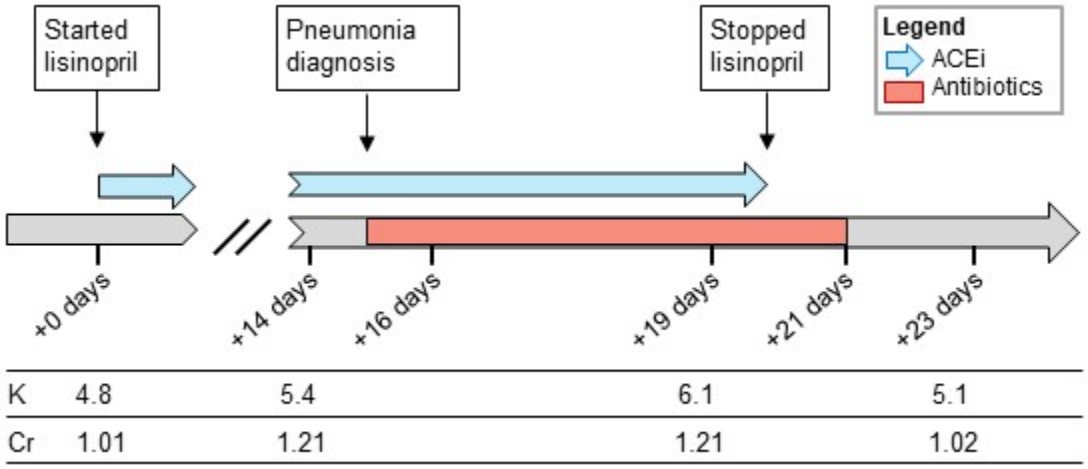


Figure 1. Timeline of clinical course. Cr: Serum creatinine. K: serum potassium. ACEi: angiotensin- converting enzyme inhibitor.

***Discussion***

Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are the most widely used medications for hypertension treatment both in the United States[1] and worldwide.[2] ACEi/ARB therapy may decrease potassium excretion through effects on the renin-angiotensin-aldosterone system (RAAS), primarily through a decrease in aldosterone levels. Hyperkalemia is a known complication of ACEi/ARB use. Patients in the Veterans Affairs health system reported an incidence of 2.5%[3] but the true incidence may be higher.[4] Hyperkalemia related to ACEi/ARB use is usually mild and asymptomatic, however life-threatening cases have been reported.[5]

For most patients treated with ACEi/ARB, the decline in serum aldosterone is not sufficient to significantly impair potassium excretion. Hyperkalemia from ACEi/ARB is more commonly seen when there is pre-existing decrease in aldosterone related to a disease or medication.[6,7] Risk factors for hyperkalemia with the use of RAAS inhibitors include chronic kidney disease (CKD), increased age, diabetes, heart failure, volume depletion, potassium supplementation, and the use of drugs interfering with renal potassium excretion[7] (Table 1). There is an inverse association between hyperkalemia incidence and estimated GFR.[3]

A case-control study of 1818 patients at a Veterans Affairs hospital identified 2 factors predicting severe hyperkalemia (potassium > 6.0) among patients taking an ACEi: age greater than 70 years and BUN greater than 25 mg/dL. The negative predictive value of these 2 factors for predicting severe hyperkalemia following an episode of mild ACEi-associated hyperkalemia was 97%.[4]

| **Table 1:** Risk factors for hyperkalemia with the use of RAAS inhibitors (adapted from Palmer et al.[7]) |
|---|
| Chronic kidney disease* |
| Diabetes mellitus |
| Congestive heart failure (decompensated) |
| Volume depletion |
| Increased age |
| Drugs used concomitantly that interfere in renal potassium excretion<br>Nonsteroidal anti-inflammatory drugs<br>Potassium sparing diuretics (e.g. aldosterone)<br>Trimethoprim<br>Antifungal azoles (e.g. ketoconazole)<br>Pentamidine<br>Calcineurin inhibitors (e.g. cyclosporine, tacrolimus)<br>Beta blockers<br>Heparin |
| Potassium-containing supplements |

*Risk of hyperkalemia is inversely related to glomerular filtration rate

Aging is associated with structural and functional changes in the kidney which predispose older adults to ACEi/ARB-related renal injury and hyperkalemia. Age-related kidney changes include nephrosclerosis, decreased renal mass, renal cyst formation, and an associated decrease in the number of functional nephrons. These changes lead to a GFR decline of 6.3 ml/min/1.73m$^2$ per decade.[8] Older adults also have a suppressed RAAS, with lower levels of plasma renin and aldosterone,[9] and a decreased transtubular potassium gradient.[10] These changes are associated with an increased risk of fluid, potassium, and other electrolyte abnormalities in older adults. The risk of hyperkalemia is enhanced when medications (e.g. RAAS blockers, NSAIDs) further inhibit potassium excretion.[9]

There is widespread agreement for routine monitoring of serum creatinine and potassium after ACEi/ARB initiation to identify asymptomatic kidney injury and hyperkalemia. Among patients with CKD, Kidney Disease: Improving Global Outcomes (KDIGO) recommends measurement of GFR and potassium within 1 week of starting or following any dose escalation of ACEi/ARB in patients with CKD.[11] Despite these recommendations some report, nearly one-third of patients who initiated ACEi/ARB at least 1 year previously did not undergo laboratory monitoring.[12]

This patient developed severe hyperkalemia within 1 month of starting a low dose of lisinopril. She had multiple risk factors for developing hyperkalemia, including pre-existing renal insufficiency (eGFR 51), advanced age (90 years old), and elevated BUN (BUN 26). Physiologically, the patient likely had structural changes of her kidneys and age-related hyporeninism and hypoaldosteronism, which made her potassium homeostasis sensitive to RAAS-inhibition. The patient also had a possible pulmonary infection, and inflammation may have further stressed her renovascular system. However, we do not think that infection was the primary driver of patient's hyperkalemia given mild symptoms and lack of systemic signs of inflammation.

This case highlights the importance of hyperkalemia risk assessment and monitoring for all patients being considered for ACEi/ARB therapy. Pre-treatment, this patient was identified as having no contraindications to ACEi therapy, however an integrated assessment of her age and other hyperkalemia risk factors may have prompted a decision to prescribe a lower initial dosage of lisinopril (2.5 – 5 mg daily, rather than 10 mg daily). The patient's hyperkalemia was identified through guideline-directed lab monitoring, which enabled her provider to stop ACEi treatment to avoid potassium-related complications.

***Conclusion***

In conclusion, this case brings attention to a severe side effect of a commonly prescribed medication class. Individuals at risk for ACEi/ARB-related hyperkalemia can be easily identified through careful evaluation for risk factors. Those without risk factors have low risk of clinically significant hyperkalemia. Prescribers should be aware of age-related changes in renal structure and function which makes older adults susceptible to

ACEi/ARB-related hyperkalemia and kidney injury. Individuals at risk of hyperkalemia should start at lower doses of ACEi/ARB and have close laboratory monitoring after initiation of therapy.

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