Clinical Pearls in Renal Medicine

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Disclosures

None of my financial holdings will have any influence on the topics I have chosen to present at today’s Family Medicine CME conference. I do not own any equity positions in the any of the pharmaceutical companies that manufacture the drugs I am going to discuss.

Clinical Case #1

A 54 year-old male with type 2 diabetes and early CKD stage 3 felt to be secondary to diabetic nephropathy comes to your office for follow up. BP's at home on losartan 50 mg/day and chlorthalidone 12.5 mg/day are 150/95 mm Hg. BP is 154/94 mm Hg and there is no edema. Creatinine is 1.5 mg/dL, e GFR is 52 ml/min, and urine P/C ratio is 0.8.
Clinical Case # 1: Question

Which of the following is the most appropriate next step to treat his hypertension and proteinuria in diabetic nephropathy?

- Double losartan to 100 mg/day
- Double chlorthalidone to 25 mg/day
- Add lisinopril 10 mg/day
- Add amlodipine 5 mg/day
- Add carvedilol 12.5 mg bid

Original Article

Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

- Purpose of the paper
  - Designed to test the safety and efficacy of combination therapy ACE inhibitor and an ARB as compared with ARB mono therapy
  - 1448 VA patients with type 2 DM and DN were randomized to losartan plus lisinopril vs losartan mono therapy for 48 months

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Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

- Primary end points
  - Decline in eGFR
  - ESRD
  - Death

- Secondary end points
  - First occurrence of a decline in eGFR
  - Tertiary end points
    - Cardiovascular events
    - Change the slope of the eGFR
    - Change in albuminuria in one year

- Adverse events and safety
  - All cause mortality
  - AKI
  - Hyperkalemia
    - $[K+] > 6.0$ meq/L
Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

- Study terminated early in October of 2012
- Safety concerns over the following adverse events
  - AKI
  - Hyperkalemia

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Figure 1A

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Figure 1B
Table 2

Table 3

Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy: Take home points

Recommendation: Avoid combination therapy with ACE inhibitors and ARB’s in patients with diabetic nephropathy

- No benefit in outcomes in any parameters measured
- Higher incidence of complications

Unanswered questions:

- Do these findings apply to other renal diseases and other populations other than patients with diabetic nephropathy?
- Do these findings apply to combining ACE inhibitors or ARB’s with aldosterone receptor antagonists such as spironolactone?

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Clinical Case # 2

A 51 year old Caucasian female with type 2 diabetes for 7 years and stage 3 CKD comes to your office for follow up. She is taking glyburide 5 mg/day, lisinopril 20 mg/day and chlorthalidone 12.5 mg every other day. Her BMI is 34, BP is 130/85 mm Hg, and there is no edema. Creatinine is 1.3 mg/dL with an e GFR of 46 ml/min. Hgb A1C is 8.1%.

Clinical Case # 2: Question

Which of the following would you do to treat her diabetes and lower her Hgb A1C?

• Double glyburide to 10 mg/day
• Discontinue glyburide and start glipizide at 20 mg/day
• Begin insulin therapy
• Begin metformin at 500 mg/day and increase to 2000 mg/day to achieve target A1C

Metformin in Patients With Type 2 Diabetes and Kidney Disease
A Systematic Review
Silvia E. Itamura, MD; Kasia J. Lipka, MD, MHS; Helen Maye, MLS; Clifford J. Bailey, PhD; Darren K. McGuire, MD, MHS

Purpose of the Paper

• To review whether or not there is truly an increased incidence of metformin associated lactic acidosis (MALA) in patients with impaired kidney function.

65 papers selected between 1950-2014 that were of the following categories:
• Pharmacokinetic/metabolic investigations: 10
• Case series: 20
• Cross-sectional, observational, and pharmacosurveillance: 31
• Meta analyses: 3
• Clinical trial: 1

Current labeling guidelines from the FDA
Metformin in Patients with Type 2 Diabetes and Kidney Disease: A Systematic Review

- Although metformin clearance is decreased in CKD, drug levels remain within the therapeutic range when the e GFR is > 30 ml/min
- No consistent link between metformin and lactic acidosis has been found
- Incidence of lactic acidosis is rare
- Frequency of lactic acidosis in patients taking metformin is very low

Conclusion from the data reviewed:
- As long as kidney function is stable and the patient is observed closely, metformin is unlikely to measurably increase the risk of lactic acidosis in those with mild to moderate CKD
- e GFR: 30-60 ml/min

Table 2
### Expanded use of metformin in patients with CKD:

**Take home points**

- Drug levels and lactate levels in patients with stage 3 CKD generally remain within the therapeutic and normal range, respectively.
- The overall incidence of lactic acidosis in metformin users is indistinguishable for the background rate in the overall population with diabetes.
- Observational studies suggest a potential benefit from metformin on micro-vascular outcomes in patients with CKD.
- Caution: No benefit in macro-vascular complications when A1C is “Optimal” at 7.0%.
- Expansion of metformin use in patients with Stage 3 CKD seems appropriate given the potential benefit and over the implied risk.

### Clinical Case # 3

A 45 year old male with CKD stage 3 is seen in your office for a routine appointment. He is feeling well and has no complaints. Current medications include lisinopril, insulin, amlodipine, and spironolactone. PE reveals a BP of 131/80 mm Hg. There are no crackles and there is no edema. Labs reveal [K+] of 5.9 meq/L. Urine protein/creatinine ratio is 0.4. Creatinine is stable at 1.7 mg/dL.

You counsel him on dietary K+ intake and prescribe chlorthalidone, 12.5 mg/day.

He returns 4 weeks later without any complaints and he states he has implemented the dietary and medication change(s) from the last visit. [K+] in 5.6 meq/L.

### Clinical Case # 3: Question

Which of the following would you recommend next to treat his hyperkalemia?

- Stop the lisinopril
- Stop the spironolactone
- Prescribe Sodium polystyrene sulfonate (Kayexalate)
- Prescribe Patiromer 8.4 grams bid
- Double the chlorthalidone to 25 mg/day
Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

• Purpose of the paper

• To evaluate the safety and efficacy of patiromer in patients with chronic kidney disease who were receiving at least one RAAS inhibitor and who had hyperkalemia.

What is Patiromer?

• Patiromer

• Non absorbed spherical bead that binds potassium in exchange for calcium

• Works predominantly in the distal colon

• FDA approved for the treatment of hyperkalemia in 2015

• Very little of the drug is absorbed so little calcium is absorbed
Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

• Study design
  • Single blind treatment phase for 4 weeks
  • 4.2 or 8.4 grams of Patiromer initially
  • Up to 21.4 grams needed to achieve goal [K+]
  • Placebo controlled randomized withdrawal phase for 8 weeks
  • Patiromer or placebo
Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

- Safety and tolerability
- Monitoring of adverse events
  - Hypokalemia: 3.0%
  - GI side effects: Most common
    - Constipation: 11%
    - Diarrhea: 3%

New therapies for the treatment of hyperkalemia: Take home points

New agent FDA approved in 2015: Patiromer
- Allow patients to safely continue RAAS inhibitors that seem to benefit them the most
- Poised to replace resin therapy as a safe long-term oral therapy for hyperkalemia
- Unanswered questions
  - Will this agent be useful in treating acute hyperkalemia?
  - Will the potassium lowering effect be maintained for greater than 28 days?
- Long Term Safety profile: Unknown
Learning Objectives

At the conclusion of this activity, members of the audience will be able to:

• Apply the principles of EBM to make decisions about the dual blockade of the RAAS in treating patients with hypertension or CKD with proteinuria
• Determine which patients with type 2 DM and CKD would benefit from the use of metformin without the risk of lactic acidosis
• Evaluate the safety and efficacy of a new oral medication approved for the treatment of hyperkalemia

Conclusion

• Combination angiotensin inhibition for the treatment of diabetic nephropathy has no proven benefit and increases the risk for AKI and hyperkalemia
• Expanded use of metformin in CKD stage 3 appears safe and awaiting FDA approval for expanded use in this patient population
• Newer therapies for long term treatment of hyperkalemia may allow for ongoing use of agents that block the RAAS that are often prescribed in CKD