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Considerations When Using a Potassium Binder in Patients with CKD

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Considerations When Using a Potassium Binder in Patients with CKD” is provided by Medtelligence.

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Dr. Epstein:
Determining of the optimal response to hyperkalemia in patients with chronic kidney disease can be truly challenging. However, today in 2021 and 2022, we have new, novel potassium binders and recent changes to accompany that in guideline-directed medical therapy offering, really, new windows of treatment for patients with a wide array of chronic kidney disease [CKD]. So what our therapeutic rationale should be is to manage chronic or recurrent hyperkalemia to improve outcomes in patients with CKD. That’s really the goal of our program today.

So this is a CME program on ReachMD. Allow me to introduce myself and my colleague. I’m Dr. Murray Epstein, from the University of Miami School of Medicine, the Division of Nephrology, and I’m joined today with Dr. Gates Colbert, who is affiliated with Baylor Scott & White and is a faculty member in the nephrology division at Texas A&M University School of Medicine.

Dr. Colbert:
Thank you, Murray. It’s a pleasure to be here today.

Dr. Epstein:
Gates, some of the most challenging patients that we have are CKD complicated by recurrent or, in some instances, sustained hyperkalemia. What recent changes would you point to in the treatment paradigm that will essentially inform and steer the trajectory of our treatment paradigm?

Dr. Colbert:
So looking historically, we know that CKD is your highest disease risk factor for having hyperkalemia because so much of our potassium’s eliminated from the body through the kidney. And the major disease states that we see that lead to hyperkalemia are chronic kidney disease, heart failure, and diabetes, and unfortunately, a lot of these disease states run together. So this stacking of risk factors goes higher and higher as you have all of these disease states. And then additionally, we know from studies that are 20 years old and some newer ones, that maximizing RAAS [renin-angiotensin-aldosterone system] inhibitors is the best way that we’ve had so far to try and slow the progression of CKD, but also we know that adding RAAS inhibitors raises the potassium as well. So we’ve been stuck with this problem of how are we going to maximize the effectiveness of the medication regimen and control potassium. And then we have, in 2020 and 2021 going forward, we have seen major clinical trials show that using SGLT2 inhibitors, as well as the new MRA, finerenone, as a huge add-on to our baseline of maximal RAAS inhibition, and we’ve been able to see in both types of medication classes a dramatic reduction in CKD progression moving to dialysis and proteinuria reduction. And so it’s a very exciting time, and we’ve been waiting, you know, multiple decades for some advances, and we’re finally seeing them, in rapid progression here, in the last 12-24

months.

Now one thing that we have to be wary of and just be mindful, is that when we add one of the additional SGLT2 inhibitors or an MRA to a maximal RAAS inhibition, is that hyperkalemia can be a risk for some patients. And so we need to be thinking about that in some high-risk patients, but it's also very nice, in 2021, that we have effective potassium-blocking and potassium-controlling medications available to help these patients.

Dr. Epstein:
Thank you very much, Gates. As you indicated RAAS therapy has the potential to markedly improve outcomes in patients with CKD, and so in order to complement the comments that you made in your description, which was spot on, I'd like to have the audience join us in watching a video to further understand what's going on in these patients, essentially a video on the mechanism of action of how these medications work.

[VIDEO PLAYS]

Announcer:
Aldosterone is the key regulator of potassium homeostasis and urinary potassium excretion.

In the absence of therapeutic intervention, conditions such as CKD and heart failure can lead to retention of potassium through the renin-angiotensin-aldosterone system, or RAAS.

If RAAS activity is unimpeded, it can lead to harm in the kidneys, heart, vasculature, and brain. RAAS inhibitors, or RAASi, are beneficial in CKD and heart failure but can lead to challenges of their own and further promote hyperkalemia by reducing aldosterone production and inhibiting aldosterone activity.

CKD and RAAS inhibition can both reduce renal potassium excretion, which increases potassium in the colon.

Dr. Colbert:
So given this current focus on the treatment of patients with hyperkalemia, our goal is to avoid down-titrating or stopping completely RAAS inhibitor medications. So, Murray, can you explain the therapeutic rationale for using these potassium binders to improve our patients' outcomes?

Dr. Epstein:
Gates, that's really a great question. Essentially, our goal as clinicians is to meet the mandated guidelines and to sustain treatment in the patient with CKD.

Very simply, the 2 events that we wish to prevent are down-titration and discontinuation. And the pivotal word is "sustain." So with that in mind, I'd like to share with the audience, the second portion of the video, which will deal with and focus on these differential effects of the available potassium binders.

[VIDEO PLAYS]

Announcer:
RAASi therapy is critical for long-term care of CKD and heart failure. However, RAASi-induced hyperkalemia is often managed by discontinuation or down-titration of therapy, despite the recommendation of Guideline-Directed Medical Therapy.

The use of novel potassium binders is the only way to maintain optimal RAASi dosing and reduce hyperkalemia. Patiromer and sodium zirconium cyclosilicate, or SZC, are FDA-approved novel potassium binders. They can achieve sustained normokalemia without the complications of earlier binders.

Patiromer captures potassium in the lumen of the GI tract and exchanges it for calcium. This increases fecal excretion of potassium and lowers free potassium in the GI lumen and in serum levels.

Because patiromer may also bind magnesium in the colon, some cases of hypomagnesemia have been reported. This can be managed with magnesium supplementation.

SZC also captures potassium in the lumen of the GI tract, leading to the fecal excretion of potassium. However, SZC exchanges potassium for hydrogen and sodium. The hydrogen may contribute to SZC having a more favorable effect on acid/base status.

Because of its mechanism of action, SZC can lead to increased sodium absorption, which may be of concern due to edema and reduced efficacy of RAASi therapy.

Novel potassium binders such as patiromer and SZC allow most patients to remain on their RAAS inhibitors for sustained periods of

time.

Dr. Epstein:
So for those of us who are just joining this CME on ReachMD, I'm Dr. Murray Epstein from the University of Miami, and I have the pleasure of being joined here with Dr. Gates Colbert, from Baylor Scott & White and Texas A&M University School of Medicine. And what we're discussing here is the role – really, I should say the emerging role of potassium binders in enabling sustained treatment with MRAs with maximal RA blockade in patients with CKD.

Dr. Colbert:
So, Murray, let's focus now on how these different potassium binders are not the exact same medication. They are not copycat medications. They work in a different mechanist of action. And they have different counter cations that are bound to the different medications. And this may have some major implications in how they work and potential long-term outcomes. What do you see as big differentiators between patiromer and SZC [sodium zirconium cyclosilicate]?

Dr. Epstein:
Well, thank you, Gates. I think that's a very important issue, and actually it's one that we are very interested in, in terms of currently investigating. We have 2 counter cations – sodium and calcium. And the street talk, if I could use the slang, was that the concern with the sodium cation was edema. And indeed, if you have increased sodium acquisition to a patient with heart failure or CKD, they're more apt to retain that and to have edema. But I think that's overly simplistic. If the only price we had to pay for sustaining MRA and RAAS inhibition was having the patient buy a larger size shoe, I wouldn't be that concerned. But it's more than that. Going back to post hoc analyses, what they basically showed is if you have RAAS inhibition, if you then do that in the setting of either high salt, medium salt, or low salt, very simply, patients on a higher sodium intake and a more sodium certified state, will have less efficacious RAAS inhibition. Very simply, sodium aboard is a determinant of whether RAAS inhibition will work maximally or so-so. And I think it's a very important issue, and we're very taken with that. So something to keep an eye on going forward, and I think it may very well be important.

Dr. Colbert:
Yes, I fully agree. I think that's wonderful.

Dr. Epstein:
So to provide an evidence-based platform, Gates, can you share with us 2 or 3 studies that you think are pivotal, that really touch on that, and can convey to the audience the evidence base that allows us to say what we're doing about the potassium binders?

Dr. Colbert:
Yes, absolutely, Murray. The nice thing about our new oral potassium binders is they've had to go through rigorous trials and investigation to get FDA approval. So we have a lot of great data that shows safety, efficacy, and even better, potential outcomes for our patients. So when we look specifically at patiromer, there were 2 big trials that have great importance. The OPAL-HK trial, which was a 12-week trial that really was looking at dose finding for giving patiromer to patients. And they showed that a single- or double-dose of patiromer was well tolerated over 12 weeks, and when it was compared with placebo, it had a big change, a significant change in controlling potassium up to 1 milliequivalent from a change in baseline at 4 weeks, and then 0.7 milliequivalents at a change of 12 weeks. So we saw a major difference with giving patiromer versus placebo to control hyperkalemia.

Then the longer-term safety trial, the AMETHYST-DN trial, this looked at 52 weeks of giving patiromer at different doses for patients. And additionally, we saw control of potassium for the entire year. We saw good safety data and high tolerability for the entire year as well. There was very, very little hypokalemia, which is also important because the potassium mortality is a U-shaped curve. When it goes really high, mortality goes up, and when the potassium goes really low, mortality goes up as well. So you want to maintain that potassium within a safe range.

Additionally, we also have great placebo-control trials with SZC, or sodium zirconium cyclosilicate. So there are several trials. They were looking at efficacy and dose finding as well. There was a 2-week trial with SZC that showed, at different doses, as the dose went higher of SZC, our potassium change was better and better over that time.

The probably more well-known trial is the Harmonize trial. And this trial looked at outpatients, 258 patients, and they gave SZC 3 times a day for up to 48 hours. And we saw that at different doses, potassium went lower and lower. And this was well tolerated by patients overall and also had good safety.

Additionally, there are further ongoing trials with these medications that are going to be some interesting results to see how it can continue to further expand the use of the different potassium binders with RAAS inhibition.

Dr. Epstein:

Okay, thank you very much. I think that was a very good summary.

All right. So it's been a real pleasure to join with Gates Colbert on this CME program. I want to thank our audience for their interest and for being with us throughout this CME program. And before we wrap up, I'd sort of like to leave the audience with what we as the faculty think may be 2 major take-home messages. Gates, would you like to start off with that?

Dr. Colbert:
Absolutely. So I think that going forward, we need to think of these potassium binders as working synergistically with maximizing RAAS inhibitors and adding on MRAs or even SGLT2 inhibitors. They work together, they have great outcomes, and I think we're really going to see some great improvement in our clinical outcomes long term with these patients.

We need to get away from thinking of oral potassium binders as only a rescue medication when things go awry. They are more than just rescue medications, and we have good data to prove that they can have major impact on clinical outcomes.

Dr. Epstein:
Thank you very much. I fully agree with that. Let me add one other thing, which has certainly mesmerized me. Again, I'm absolutely enthused on the fact that we're on the top of a wave, with new modalities that essentially can convey major benefits to morbidity and mortality in – we're talking about hundreds of millions of patients who we know globally have CKD and diabetes mellitus with CKD. We now have the wherewithal of several classes of medications, most recently the SGLT2 inhibitors and now finerenone. All of these, and all of the basic messages and mandates of these studies can only be implemented if we're able to cope with and to sustain normokalemia. And indeed, the major message of our CME program today is that now we are. We are fully equipped and adapted, with the 2 novel potassium binders, to be able to sustain long-term normokalemia, therefore enabling sustained RAAS and MRA treatment.

Again, I want to thank my friend and colleague, Gates Colbert, and the producers of this ReachMD program, and it's been a pleasure to be able to share with you a new, evolving area of nephrology that we're very enthused about. Thank you again.

Dr. Colbert:
Thank you, Murray, and we appreciate everyone for tuning in.

Announcer:
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