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Case-Based Management of Hyperkalemia to Optimize RAASi Therapy in Patients with CKD

Announcer:
Welcome to CME on ReachMD. This activity, titled "Case-Based Management of Hyperkalemia to Optimize RAASi Therapy in Patients with CKD" is provided by Medtelligence.

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Dr. Kosiborod:
Chronic kidney disease, or CKD, and hyperkalemia, an abnormally high potassium level in the blood, are a dangerous duo. While the renin angiotensin aldosterone system inhibitor, or RASi treatment, is recommended for CKD management and can offer significant benefits, it's optimal use in patients with hyperkalemia presents a unique set of challenges.

This is CME on ReachMD and I'm Dr. Mikhail Kosiborod.

Dr. Palmer:
And my name is Dr. Biff Palmer.

Dr. Kosiborod:
It's always a pleasure to be with you. Modifying RASi treatment in patients with CKD to manage hyperkalemia can potentially be associated with worse patient outcomes. What exactly are the potential risks that you can tell us about that are associated with this approach?

Dr. Palmer:
I agree with you, totally. You know, the traditional response of many clinicians in practice is, whenever they encounter hyperkalemia in patients who are being treated either with an ACE inhibitor, ARB, or an aldosterone antagonist, the traditional response is to down-titrate or even often times discontinue the drug. The dilemma that's created by that is, remember that those drugs offer a great deal of cardiovascular protection and as a nephrologist, we use ACE and ARBs as antiproteinuric effects. So, the downside risk of not using optimally dosed medications is that you lose those cardiovascular benefits. And you know, if we could have a way to be able to enable the usage and yet manage the hyperkalemia, this would be a great therapeutic benefit.

Dr. Kosiborod:
In the past beyond dietary modifications and down-titration and discontinuation of RASi, as there were few therapeutic options because the older potassium binders were not really tolerated as a long-term treatment by many patients, but now we have additional options, which we'll get back to in a minute. But just to follow-up on where we are today, what do the current renal practice guidelines, such as those from KDIGO say about how to handle RASi treatment in the clinical setting like that?

Dr. Palmer:
The most recently KDIGO Guidelines for management of chronic kidney disease, as well as management of blood pressure. They specifically state that one should at least think about using, for example, these potassium binding drugs as a way to manage

hyperkalemia. And they advocate to minimize the tendency to either down-titrate or discontinue the ACE or ABR therapy that would be present in those individuals.

Dr. Kosiborod:
I know that the tolerance level for potassium elevations sometimes differs across specialties, and it's not uncommon to see, clinicians potentially, one could argue, overreact and discontinue RASi treatment, or maybe down-titrate RASi treatment, even in the setting where potassium levels are just mildly elevated or moderately elevated, you know, somewhere in the low to mid-5 range, in terms of milliequivalents per liter where I believe nephrologists tend to have much higher tolerance. What is your take in terms of as the level potassium elevation and how it should impact clinical decision-making, especially when it comes to modification of RASi treatment?

Dr. Palmer:
That's a great question. Let's say you feel comfortable between a 5 and a 5 and a half, how do you know that, for example, in the postprandial period after a meal that you don't have a major excursion into a much higher value that you'd be much more concerned about. So, I guess I've become a little bit more conservative over time and try to intervene at levels that are a little bit lower than perhaps what I've done in the past because of these potential excursions.

Dr. Kosiborod:
There is continuous debate between different viewpoints in terms of epidemiologic relationship between potassium elevations and worse patient outcomes. I think it's very clear from observational studies that even relatively mild elevations in potassium levels are associated with worse patient outcomes. The big question, of course, is whether it's due to the potassium levels themselves, or is it just higher risk patients that tends to develop those potassium elevations, or does that elevation in potassium levels actually result in clinical decision-making, such as discontinuation or down-titration of RASi treatment, which may have the risks of its own. We have other potential treatment options now that we can potentially implement in practice.

So, I know you have a case for us to outline the management of hyperkalemia associated with RASi treatment in patients with CKD. So, perhaps let's go over that case now, Biff.

Dr. Palmer:
It was a 58-year-old man. He had a longstanding history of hypertension. He had stage 3b chronic kidney disease. And he had a low grade of proteinuria. His baseline creatinine was 1.6, so relevant to our discussion, he was on an ACE inhibitor, ramipril, chlorthalidone, carvedilol, and amlodipine. Now, despite being on, really, 4 different medications because of his underlying diabetes and chronic kidney disease, his blood pressure still wasn't really where I wanted it to be. At when I first saw the person, his blood pressure was 150/92 mmHg. And so I decided to add spironolactone because, as you well know, spironolactone can sometimes be quite useful in so-called drug resistant hypertension.

And indeed, after starting the medication, I got a very good response. His blood pressure upon follow-up was now lowered to 132/82. The problem was that his potassium was, as I mentioned, at baseline was 4.8, but then when I rechecked it in follow-up, it had gone up to 5.6. So, again, here is a patient representative of the dilemma I spoke of, and that is, I had a good therapeutic response with this additional renin angiotensin aldosterone blocker, but now I have a metabolic side effect, that being a hyperkalemic response of value that, again, with my current – my own personal threshold, I felt a little bit uncomfortable with. So, the question was, do I want to stop the spironolactone and give up on the better blood pressure control, or might this be in fact a patient I would consider keeping on those medications, but then add a potassium-binding drug, again, to enable the utilization of the aldosterone blocker?

Dr. Kosiborod:
Now, we know that kind of, older traditional potassium binders, they tend not to be very well tolerated as long-term therapies. But we do have novel potassium binders now that appear to be better positioned for chronic use and these are sodium zirconium cyclosilicate, or SZC, and patiromer. What do we know about SZC in terms of it's affect on potassium levels from the clinical trials that have been done, both on the efficacy side and then what do we also know about the tolerability side of the equation?

Dr. Palmer:
With regards to the zirconium cyclosilicate, as you know, it was devised as a crystalline structure that's highly specific for potassium. The only other thing it seems to bind to is ammonium. It binds potassium in exchange – and it liberates a little bit of sodium. It seems to be quite effective. We have data that when you start the agent as prescribed, which is 3 times per day for 48 hours and then transition the patient to once a day thereafter, that's the way it was done in the clinical trials. Basically you get a nice drop in the plasma potassium as early as one hour after administration. And then there are data to show that when used over a 1-year period, you have a durability of effect with continued control of the plasma potassium. I think, in the trials, it's noteworthy that about two-thirds of the patients were receiving renin angiotensin system blockers. So, it's consistent with this idea that this might be a way to be able to control plasma

potassium and enable the ongoing use of renin angiotensin system blockers.

As I say, the side effect profile of the zirconium is quite good. The thing that's really been noted is that at the 15 g dose, which is not commonly used there was a small amount of edema but that was typically seen at that much higher dose. It's been debated as to how much of that sodium is actually absorbed. One of the things that is noteworthy is that it's actually indicated for control of pre-dialysis hyperkalemia. And in that population, there's been no changes in interdialytic weight gain or worsening blood pressure control, again, arguing against a significant amount of salt absorption when using the drug.

Dr. Kosiborod:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Mikhail Kosiborod, and here with me today is Dr. Biff Palmer. We're discussing management options to manage hyperkalemia in patients with CKD and it's associated comorbidities, while maintaining guideline recommended RASi treatment.

There is a REALIZE-K trial that's going on where it's the trial is evaluating whether use of SZC could potentially enable better optimization of guideline-directed medical therapy in patients with heart failure and reduced ejection fraction who cannot tolerate or, previously didn't tolerate, MRA such as spironolactone due to hyperkalemia or considered to be at high risk for hyperkalemia. And that trial is currently ongoing, and I think those results will be very interesting.

There is, of course, another novel potassium binder, as I mentioned before, patiromer, and there are a number of trials looking at patiromer efficacy as well. That's an inorganic polymer that exchanges sodium for calcium. And those studies also show that patiromer is efficacious in controlling potassium levels and tends to be well-tolerated over a longer time period. So, I think we have several options in this space now, where these potential novel potassium binders can help manage this kind of a vexing issue of patients that really can benefit from RASi, but have an issue with elevated potassium levels.

The clinical trials that have been done with novel potassium binders, such as SZC and patiromer included patients that were relatively broad in terms of their baseline characteristics. There were certainly many patients in those trials that were on RASi treatment at baseline. There were patients with diabetes. Of course, many of them had significant underlying chronic kidney disease and various levels of potassium perturbations, including patients with really significant hyperkalemia potassium levels over 6 in some cases. So what we know from the efficacy trials is that these novel potassium binders appear to be overall efficacious in bringing potassium levels down within a reasonable time period, regardless of those patient characteristics, which I think is relatively broadly applicable to clinical scenarios in which we see patients that develop elevated potassium levels.

Biff I think this has been a really informative conversation. Before we wrap up what would you summarize as your kind of key take-home message to the audience?

Dr. Palmer:
Our guidelines, whether you're talking about the KDIGO, the European Society of Cardiology really pushed the idea that we should not be down-titrating or discontinuing renin angiotensin system blockers until we've really exhausted all approaches. And with the new availability of these tolerable potassium-binding drugs, it's really provided a new tool that has been quite effective in enabling us to use guideline-directed renin angiotensin system aldosterone blockade.

Dr. Kosiborod:
There are many patients that are not optimized on GDMT, or guideline-directed medical therapy. It's frequently because of underlying chronic kidney disease and risk of hyperkalemia, especially when it comes to medications like ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists.

In the past we really had relatively few treatment options, but they're expanding, which is really good from a clinical practice standpoint, both for our patients, and for us as clinicians. And we should think about these different therapeutic options, which now included novel potassium binders that have been studied in clinical trials.

That's all the time we have for today, so I want to thank our audience for listening, and thank you, Dr. Biff Palmer, for joining me and for sharing all of your valuable insights. It was really great speaking with you today.

Dr. Palmer:
Well, thank you very much. It was a real pleasure.

Announcer:
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