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Potassium Binders Facilitate Continued RAASi Therapy: Helpful Tips for Clinicians

Announcer:
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Dr. Piña:
Hello. Welcome to our discussion entitled *Potassium Binders Who Facilitate Continued RAASi Therapy and Helpful Tips for Clinicians*. I’m Ileana Piña. I’m professor of medicine at Central Michigan University, and I’m joined today by my good friend and colleague, Javed Butler from the University of Mississippi in Jackson, Mississippi. Welcome, Javed. Thank you for joining me.

Dr. Butler:
My pleasure. Great to be with you, Ileana.

Dr. Piña:
So let’s start out with a case because I think cases are great for discussion. So here’s a 63-year-old African American lady who has a history of 3a CKD and her eGFR is about 48. She has HFrEF with an EF of 38%, history of hypertension, weighs 79 kilos, and has a BMI of 30. That’s not unusual, as you know, in our clinics. She is on the following meds: She is on carvedilol 50 bid. She’s on good doses of candesartan at 32 mg daily. Spironolactone 25 mg once daily. And she’s on a little bit of torsemide, 20 mg daily. Her potassium at this point is 5.3. Her sodium is fine; it’s 138. And the blood pressure is still elevated 147/78, with a heart rate of 65. Her lungs are perfectly clear, and she has just a tiny little bit of peripheral edema. That’s really not that important.

So, Javed, this is probably not a nontypical case. What do you think, just hearing this?

Dr. Butler:
The one thing you mentioned is this person’s potassium is 5.3. A lot of times these potassiums come back when they come for their routine labs, not necessarily any symptoms or anything like that. And one thing that comes to mind is to just make sure this is not a hemolyzed sample.

Dr. Piña:
Yeah. So it was verified. The sample was not hemolyzed. She has no symptoms that would resemble a hyperkalemia-induced arrythmia, paresthesias, nausea, vomiting, or any other symptoms. However, the decision was made to cut the doses in half for both the candesartan and the spiro, and then she was put on amlodipine at 5 mg daily and the potassium did come down to 4.7, like, in about 5 days after that follow-up. However, now she got lung congestion. Now she has peripheral edema, which very often may be the amlodipine, as a matter of fact. She was hospitalized now with acute decompensation about 10 days later. Her potassium was 4.8 but her blood pressure was now 160/84, and what they did in the hospital was just bump up the amlodipine, which made the peripheral edema worse. So I think we can assume that gradual progression back to a decompensated state was the result of the decrease in RAASi therapy. What do you think at that point? Let’s talk about why it’s important, first of all, to start the RAASi and then try to keep it.

Dr. Butler:
Whether they are cardiology guidelines or other specialty guidelines, US guidelines, national guidelines, everybody gives a class 1 recommendation for a person like this to get RAAS inhibitor therapy. This is because there is clinical trial-proven evidence that these therapies reduce the risk of mortality and progressive worsening of comorbidities. And on top of that you need to give them at doses that were tested in the clinical trial because the higher the dose, there is incremental benefit. The history that you describe is really typical. You stop the medication or you lower the dose, and you're basically exchanging a short-term problem for a long-term problem. You're avoiding the complications of hyperkalemia, but you're now taking on all the complications of worsening comorbidities.

Dr. Piña:
Yeah, and what I have noticed, very often, the house staff may send the patient home after they diurese them in 3 or 4 days, and they never see what happens, truly, when that RAASi goes. And I find that in about 48 hours, when you start to get the kick of angiotensin 2 back, the sodium starts to plummet. And that may be the very first sign to me, as a clinician, that that patient is going to get in trouble. I think the importance, not only of starting these drugs, up-titrating them, as I think you made the really good point, and trying the hardest that we can to keep them on at the doses. This lady still has high blood pressure. Even on 32 of candesartan, which is really a pretty hefty dose of candesartan. So what do you think our obstacles are?

Dr. Butler:
Well, there are many obstacles, right? In order for them to go on optimal medical therapy, there are all these issues related to subjective tolerability, so side effects and whatnot. But also, there are objective things, right? Blood pressure, heart rate, depending on the various different drugs, creatinine, renal function, and as in this case, hyperkalemia. So hyperkalemia affects, again, 10% to 20% of the patient population. The more the comorbidity burden, the older the patient, the more the RAAS inhibitor therapy, the higher the risk. But remember that all of these studies are time-limited. So if I say 10%, 15%, well that depends on the duration of that study. But if you follow the patient longitudinally, sooner or later as people age and as their renal function continues to deteriorate, the large proportion of the patients sooner or later will run into this issue of hyperkalemia as well.

Dr. Piña:
We often see patients much older than this. What do you think of 5.3, does that scare you?

Dr. Butler:
Well, before I answer this question, I do want to expand on something that you said. This multi-morbid patient population, these are the patients that require RAAS inhibitor therapies more. So the people who are at the highest risk for developing hyperkalemia are the ones who need the therapies the most.

Now, coming back to your question, whether a 5.3 is important or not. Because it's not an issue of just a medical necessity. Remember that there is a lot of social issues that come into play, whether the patient is reliable in terms of the follow-up. How far does the patient live? Do they have family members that can bring them for repeated lab checks? The problem is going from completely okay to not okay and having arrythmias and whatnot. That transition can occur relatively very rapidly. So yes, 5.3, some people may argue is a place where we should act, and others may argue that no, maybe we should wait for more than 5.5. But that debate needs to be put into perspective of the patient not only the medical issues. And if you look at what actually happens in the clinical practice, anything over 5, clinicians will cut back the medications, and I really cannot blame them if you're not totally confident that the patient will follow up closely.

Dr. Piña:
Yeah, and you know, in our fractured healthcare system, the patient who first gets seen and her RAASi gets cut down, that clinician may not see the patient again for 2 or 3 months. We really want people to think about close follow-up of these patients. If the patient can't come in to get their potassium checked, can I get a home care type of service that will draw the potassium in the home? And I think this is also an important time when you're questioning whether the patient can come back for recheck or not, is to talk a little bit about the diet. The diets are varied by culture. Being a Hispanic, for example, I can say, you know, I want you to eat less bananas, but maybe they're eating plantains, which have more potassium than bananas. So there has to be some education about this and we have included dietary guides for potassium-containing foods in our patient education booklet.

Now, the other issue here is that this lady is obese. Her BMI is 30. Do you think that there is a relationship between obesity and the RAAS system?

Dr. Butler:
So adipose tissue is sort of a factory for inflammation and for adipocytokine production and for oxidative stress, and these things can secondarily lead to RAAS activation. But then obesity is also linked to other comorbidities like chronic kidney disease and heart failure.

Dr. Piña:
I think you were involved in the BIOSTAT data, weren't you? A huge number of patients and I don't think that years ago we were talking much about what happens with withdrawal of RAASi. Tell me a little bit about your comments on that BIOSTAT dataset.

Dr. Butler:
The clinical trials clearly show that giving the medication is good because it reduces the risk of morbidity and mortality. And then giving it at higher doses, the doses that were tested in the clinical trial, also makes things better and reduces the risk of cardiovascular death and heart failure hospitalization. But then the question comes up, what happens in the real-life patients, not in the clinical trial setting? So you know, there are multiple studies out there. BIOSTAT is one that you mentioned. If people are at less than 50% of the doses that they are supposed to be on, their risk of mortality and morbidity goes up pretty high. So that's the problem of cutting down the doses of these patients because of the medication tolerability issues or side effects. You withdraw the therapy; you put the patient at a substantially higher risk.

Dr. Piña:
Totally with you. We were going to talk a little bit about levels. When do you start, you personally with your own patients, when do you start to get worried about the level?

Dr. Butler:
So 5.5 and above absolute yes with everybody, and I would cut down the dose unless and until some of these new therapies are available to the patient like potassium binders. Between 5 and 5.5, you can kind of sort of argue that epidemiologic studies would suggest that you're much better off in the mid-4, high-4 range and not even leave the patient at 5. So, again, depending on the patient's situation, 5.1, 5.2, you might want to watch the patient carefully if you think that they are going to follow their diet and that they will follow up regularly and they will get their labs checked.

Dr. Piña:
Yeah, I have always tried to push my potassiums in my patients to around 5. Why? Because I believe that there is an anti-arrhythmic affect to get them up there. And I would not be very concerned with 5.3, but I would repeat it, I think as we were talking about, to make sure that I've got an accurate number and have that conversation with the patient. And if I were going to cut anything back, I may cut the spiro by half because I think the spiro is much more likely to be causing the hyperkalemia, if you want to call it that. Probably 5.5 would be the place that I would really get concerned. And I think there's a little bit of difference across the pond as to how the Europeans think of it and how the US thinks of it. The KDIGO guidelines has just a wonderful guide by different levels of potassium that I would recommend to any clinician to really, really take a look at this. Do you have any more comments about the KDIGO guidelines?

Dr. Butler:
No, I completely agree with you. There was also a consensus paper that came out in the *Journal of the American College of Cardiology* recently. So there are those guidelines available that can put it in the clinical perspective.

I do want to highlight a couple of points that you just mentioned. One is that if you really are in a bind and you have to do something, then cutting the dose is better than stopping it altogether. So that's one thing. And then also, something that a lot of clinicians don't realize, is that beta blockers can also cause hyperkalemia.

Dr. Piña:
Totally, and at some point, the SGLT2s are going to come in here, somewhere. You know we've never used the terminology "enabling" for RAASi therapy. And yet our oncology colleagues enable the use of their drugs by giving the patient antiemetics. So I see this as very parallel to now starting to use potassium binders. We have three of them. One that I think is just awful on the gut. But at least we have 2 that are highly tolerable and that could be used, for example, in this patient if that potassium goes up any higher or if you're uncomfortable at 5.3.

So let me ask you about the potassium binders that we have now.

Dr. Butler:
Yeah, no, I completely agree that this concept of enablement is, you know, in other specialties and even in cardiology, right? Technically speaking, if somebody has low blood pressure and you want to give them an ACE inhibitor and you cut down the dose of diuretics, that's basically enablement. So it's the same concept, but we haven't used that terminology. But now we're thinking more about it with the potassium binders.

So you know these two new potassium binders are not new. In fact, we had SPS [sodium polystyrene sulfonate], but the problem with SPS is that there's no long-term studies. Tolerability long-term is really difficult and then you have some serious side effects like colonic necrosis. So it was really not a good option. But now we do have two therapies available, patiromer and sodium zirconium cyclosilicate.

There are studies in CKD patients, heart failure patients, acute and chronic long-term management of hyperkalemia patients and then, enablement of therapy, RAAS inhibitor, MRA therapy. There are clinical trials. There are long-term registry observational studies. So there's a ton of data that have come out with these agents. And basically, we have consistently seen the same thing. Very well tolerated. We have data all the way up to a year with these agents. Then any sub-group of patient that you're concerned about, based on comorbidities, stages of CKD, hypertension, heart failure, diabetes, whether you're looking at baseline RAAS inhibitor dose, low dose, no dose, or high dose. In every individual case, you are able to manage potassium, and you're able to manage chronically hyperkalemia, and you're able to continue these therapies. And what is beautiful is that the body's own homeostatic mechanisms come into play. So the chances that you will make a hyperkalemic patient profoundly hypokalemic is really very little. Most of the patients kind of land in the mid-4 range, where you want to keep them anyway. You're able to continue therapy without compromising lifesaving medications.

Dr. Piña:
Well, I've been using them and have found them quite acceptable to the patients. I just try to tell them to take it at other times since I always try to make doses either qd or bid. For example, I love candesartan because it's once a day and it gives me, I think, better adherence to the medications. And I try to tell them to take the potassium binder at a different time so that there's no interference, even though there is no black box anymore about interference with other drugs. And I found probably most common side effect is constipation. I don't want them to stop it suddenly. If they're uncomfortable with the constipation, to call me before they do that. Because I have this fear of hypokalemia or even shooting up hyperkalemia, and it just hasn't happened. And the potassium comes down very nicely by the next morning. I usually see it at about 4.8. That's about how far it comes down, and I've usually gotten away with the lowest dose. We have to say again for transparency here, that the ZS-9 formulation at higher doses may have some sodium retention issues. But at the low doses, it doesn't seem to happen.

Now, Javed, we had a question. You and I have had a question for a while about outcomes. So if we were to control the potassium and continue the drugs and not have to remove them, would it really impact outcomes? And you are chairing the DIAMOND trial, which is the outcomes trial. Can you tell the audience a little bit briefly about DIAMOND?

Dr. Butler:
Yeah, glad to. But again, I want to highlight something that you just said, which is so crucially important. So you talked about not just stopping the drug if somebody has GI side effects. I would even extend it to say that if you start these medications and now you are able to use RAAS inhibitor therapy and the person is not hyperkalemic and you have mitigated the risk of hyperkalemia, and at the same time given the patient the benefit of good medical therapy, that doesn't mean that the phenotype of the patient that develops hyperkalemia has gone away. And what we are seeing is that even after a year of control, you stop these binders and hyperkalemia comes back. So instructing the patient to continue the therapy and that if for some reason they're traveling or something like that and they have run out of it, call your physician to just make sure because your RAAS inhibitor therapy may have to be modified.

Now turning to the DIAMOND trial that you mentioned. So clinicians are asking the question that will the enablement improve clinical outcomes per se? So one can say, well, we have randomized controlled trials and that's why we recommend – class 1 recommendation that these therapies should be given. So it just makes a lot of sense, except that the clinical community is looking for some clinical evidence. The DIAMOND trial, looking at outcomes of patiromer-guided optimization of RAAS inhibitor therapy is ongoing. We'll wait to see what the results show.

Dr. Piña:
Well, we're well on our way on that one. And as a closing point here for our audience, it really requires a conversation with the patient. You need to find out what is going on in the home. You have to find out what they're eating. You have to make sure that they're not on some herbals or nutritional supplements, and salt substitutes are pure potassium. So those conversations need to happen. And in this older population, where there's a higher use of nonsteroidals for joint pain and muscle aches, nonsteroidals can also exacerbate hyperkalemia. So I think with all those conversations that we still need to have with the patients, I think the potassium binders are offering us an option that we didn't have before and having not to stop the RAASi inhibition.

So, Javed, I'm going to close us off with this. If you have any final thoughts, what would be your final take-home message?

Dr. Butler:
My final take-home message would be that our nephrology colleagues see hyperkalemia all the time and they think about it. Our cardiology colleagues don't think about it enough because we end up stopping all the good medications or lowering the dose and "the hyperkalemia goes away." But it really has not gone away. And when a person comes in like the case that you started this discussion with, when the person comes back with decompensated heart failure or whatever comorbidity, that's not just the natural history of the disease. That actually is hyperkalemia causing worsening disease even if potassium level at that time was not normal. So hyperkalemia-

related suboptimal therapy is a big problem and that we ought to try to optimize the medications as much as we can rather than just stopping or lowering them.

Dr. Piña:
Great final message. And I know our nephrology colleagues I think are much more comfortable already with the potassium binders because for them it may push away another dialysis session that they may have to do on a patient. So they have become much more comfortable with it and I think our cardiologist colleagues really need to look at this very carefully.

So, Javed, I want to thank you for your time, for being with us today. We hope this discussion is really very helpful for the day in, day out care of these patients, which even though difficult, is really not unusual. I leave you with that. Thank you for joining us.

Dr. Butler:
Thank you very much.

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