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Binding the Enemy! Phosphate Binders in CKD

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Episode 4

Dr. Fishbane:
This is CME on ReachMD. I'm Dr. Steven Fishbane from Northwell Health. Here with me today is Dr. Stuart Sprague. Stuart, what's the mechanism of action of NHE three inhibitors and what is the trial evidence that we have that supports their use?

Dr. Sprague:
Phosphate is absorbed, predominantly extracellular between the different GI cells and the NH three inhibitors actually bind the sodium hydrogen exchanger in the intestinal cell. By doing so, it causes a small amount of intracellular protein retention. This protein retention causes a shift or confirmational change within the cell in that you get these clot and proteins that are in the tight junctions between the cells and they bind together. And when they bind together, it blocks the phosphorus from going intracellularly. So the phosphorus that's broken down from food or the phosphate additives that are in the diet would go pet through this intracellular pathway. And by shutting it, you get a physical barrier to the actual phosphate absorption. There is a little bit of sodium retention associated with these NHE three inhibitors, but they're not absorbed and they have no effect on any other cells within the body. So it really only works in the intestinal cells in causing this closure of the tight junction.

And we now have a lot of clinical data using these things in comparison with phosphate binders, which bind phosphate, but the phosphate does not bind. It could still pass through the intracellular pathways. And it has shown that compared to the studies that we have a significant decrease of serum phosphate absorption when we use an NH three inhibitor such as tenapanor in these studies as well as we have studies where we have used them in combination with each other and there's an additive effect of using the NH three inhibitors in terms of preventing phosphate absorption.

So I do think this mechanism of action is very different than what we've been doing for decades in terms of using phosphate binders and gives us another treatment to help prevent the absorption of phosphate in our patients with chronic kidney disease.

Dr. Fishbane:
Stuart, I had a question. I think forever we've thought about phosphorus binding and because of that, meals are very tightly linked to when you're taking phosphorus binders. The mechanism of action that you are describing though is distinctly not binding the medication to phosphorus to take phosphorus away. But this is really the inhibition of absorption at the intestines, isn't it?

Dr. Sprague:
Yes, it is. I mean, again, you bring up a good point. When we use phosphate binders, we have to give them with the patient's meals, and sometimes patients may have to take two, three, or four binders with each meal, which makes it burdensome. And compliance, this is,

it's something that you take one pill twice a day, okay, it's been recommended to be given before the morning meal and the evening meal, although it doesn't necessarily have to be given with the meal because the duration of action does last beyond that. But that just makes it for a convenience of dosing, and that's how the studies were done within the FDA, but it's clearly a totally different mechanism of action. And again, it blocks the phosphate absorption as opposed to binding phosphate in not letting it be absorbed.

Dr. Fishbane:
Yeah, thank you for that. Do we know anything from clinical trials?

Dr. Sprague:
Yes. We have several studies that have looked at the effectiveness of using tenapanor in reducing serum phosphate. We have the PHREEDOM study, which is a long-term phase three trial, which is a placebo controlled trial that went out to 52 weeks. And of that, the patients who were randomized to tenapanor, 56% of them had a greater than 1.2 milligram per deciliter decrease in their serum phosphate and met the pre-prescribed endpoint for that trial.

We also had the AMPLIFY trial, which was another study that actually looked at the use of tenapanor plus a serum plus phosphate binders. And this was a four week study, and what we found is that patients who had tenor plus binder compared to binder plus placebo, we had an average of a 0.7 milligram per deciliter decrease in the serum phosphate. In both these studies, we saw a significant decrease in the number of phosphate binding pills that the patients had to take during the duration of the study, and they again met some of the predefined endpoints that were set up for the studies.

Dr. Fishbane:
Well, Stuart, thank you so much for such a clear explanation. That is our time, and thank you all so much for listening.