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Emerging Therapeutics in ADH1: Progress in Precision Medicine

Announcer:
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Dr. Schweiger:
Hello, everybody. Thank you for joining us today. My name is Michelle Schweiger, here in the Pediatric Endocrinology Program here at Cedars Sinai. And today's topic is emerging treatment options for ADH1: the therapeutic promise of precision medicine, and it's with great pleasure to introduce Dr. Michael Levine from Children's Hospital of Philadelphia.

Dr. Levine:
Hello, Michelle. I look forward to our discussion today.

Dr. Schweiger:
Thank you, Dr. Levine. I wanted to start, Dr. Levine, by asking about the identification of the calcium-sensing receptor as a site of the molecular defects and ADH1 should allow us to think about developing drugs that target the calcium-sensing receptor. Calcium mimetics, such as cinacalcet, are now used to activate the calcium-sensing receptor, and thereby reduce levels of PTH in patients with hyperparathyroidism. Are there similar approaches now underway that utilize drugs to turn off the calcium-sensing receptor and raise the levels a PTH in patients with ADH1?

Dr. Levine:
So, this is a great opportunity to talk about the calcium-sensing receptor as a therapeutic target. And you've already introduced the notion that we use calcium mimetics in order to activate the calcium-sensing receptor in patients with different forms of hyperparathyroidism. And by doing this, we can shift the sensitivity of the calcium-sensing receptor and reduce secretion of PTH, and thereby reduce serum levels of calcium.

The calcium-sensing receptor is also a target in patients who have ADH1. And here there have been developed a series of drugs called calcilytics. And these are type 2 allosteric regulators that bind to the calcium-sensing receptor and effect a rightward shift in the sensitivity curve of the calcium-sensing receptor, restoring it to a more normal sensitivity to calcium. And this allows the parathyroid gland to secrete PTH, leading to an increase in serum calcium levels.

And perhaps even more importantly, because the urine, the excessive urinary calcium excretion that occurs in patients with ADH1 is due to the presence of this same calcium-sensing receptor that has a gain of function in the kidney, the calcilytic drugs are able to also affect the sensitivity of the calcium-sensing receptor in the kidney, and this reduces urinary calcium excretion in the kidney. So, the calcilytic class of drugs in preclinical studies, and now in emerging phase 2 studies, published just a few months ago in the *New England Journal of Medicine* from the NIH, led by Rachel Gafni, show that encaleret was able to increase levels of PTH and serum calcium in 13 patients with ADH1 due to calcium-sensing receptor mutations, and at the same time, normalize the serum magnesium

level and phosphate level. And perhaps most important for patients with ADH1, encaleret as a calcilytic drug, was able to reduce and normalize urinary calcium excretion.

So, I think the calcium-sensing receptor as a therapeutic target makes a lot of sense. We've seen great success using calcium mimetics in hyperparathyroidism and now we have emerging phase 2 studies that show using a calcilytic agent, encaleret, to turn off the gain of function in the calcium-sensing receptor in ADH1, can normalize levels of PTH and calcium in the blood, and levels of calcium in the urine.

Dr. Schweiger:
Encaleret seems to increase the serum levels of PTH and calcium. But what effect does encaleret have on levels of urinary calcium in the other parts of the ADH1 equation?

Dr. Levine:
Well, this is really quite remarkable because not only can encaleret reduce the level of calcium in the urine in patients with ADH1, but there's emerging preclinical evidence that drugs like encaleret, other calcilytics, can also reduce urinary calcium excretion in animals with other forms of hypoparathyroidism, where the calcium-sensing receptor is entirely normal. And the ability to modulate the amount of calcium excreted by the kidney in patients with other forms of hypoparathyroidism, now raises the possibility that drugs like encaleret can be used as an adjunct to either conventional therapy or even parathyroid hormone, when these treatments fail to normalize urinary calcium excretion.

In addition, it's possible, if we're really dreaming here, it's possible that calcilytics may even be useful to reduce urinary calcium levels in patients with hypercalciuria, either idiopathic or due to known causes that leads to kidney stones and nephrocalcinosis, with nothing to do with the parathyroid glands.

So, these I think, are very exciting times. The identification of the class of drugs, the calcilytics and the early clinical trials of encaleret provide us with a great deal of encouragement for using these drugs in patients with ADH1, and allow us to begin to think more broadly about how drugs that modify the activity, the calcium-sensing receptor, may be used more widely in patients with other forms of hypoparathyroidism, or other forms of hypercalciuria. I think that the drugs like encaleret are going to give us a new hammer. And I think the real trick will be for us to make sure we find the right nails.

Dr. Schweiger:
So, conventional treatment with calcium and calcitriol has been the mainstay of treatment for our patients, and it has shown many benefits. Some of the pitfalls include hypercalciuria, and PTH is another treatment option, which also has hypercalciuria as a pitfall as well. Encaleret has had a phase 2 study of 13 subjects, which has been promising to show that there is significantly decreased risk of urinary calcium excretion. And so, we're going to have to look in the future and kind of see, you know, as far as further studies to see the promise in this area with this medicine.

Thank you, everyone, for joining us today. It's been a pleasure. Thank you and have a great day.

Announcer:
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