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Improving Glycemic Control: Reducing Patient Burden, The Rationale for Concentrated Insulins in Type 2 Diabetes Mellitus

Narrator:

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Here is your host, Dr. John Russell.

Dr. Russell:

A major challenge when trying to bring patients to glucose targets, for us in primary care, is the increasing need for large insulin doses. We were often uncomfortable with this for many reasons, but often because of the hypoglycemia risk.

I'm Dr. John Russell, and I'd like to welcome Dr. Anne Peters, Director of the USC Clinical Diabetes Program and professor at the Keck School of Medicine at USC. Dr. Peters is joining me to discuss two patient cases I brought to evaluate whether they are candidates for concentrated insulins.

So, Dr. Peters, thanks for being here today.

Dr. Peters:

Thanks for having me.

Dr. Russell:

So, I've got a couple cases I'd like to go over with you. The first patient is Justine. She's a 56-year-old, obese female. She's got a 12-year history of type 2 diabetes. I initially treated her with oral agents, and about a year ago I switched her to a basal bolus regimen while continuing the metformin. Throughout much of this time, she has been gaining weight. I've been titrating up her basal insulin, and we're up to about 55 units twice a day, and she's using about 30 to 40 units of rapid-acting insulin before meals. Her fasting blood glucose is about 160, her premium blood sugars are in the 120 to 200 range, and I have an A1c of 8.9. She's not had any hypoglycemic episodes, but she does admit that she has been eating some very high-carb meals.

So, given this background—clearly it seems like she has some insulin resistance—how would you recommend that I manage Justine, and do you think she'd be a candidate for one of the concentrated insulins, and how do you kind of decide with the different products we have available which might be the best one to choose for her?

Dr. Peters:

So, anybody on a total daily insulin requirement of over 200 is someone who's a candidate for U-500, and, in her case, you know that she needs more than she's on, right, because her A1c is so high.

Dr. Peters:

You've got her on 2 doses of long-acting. You've got her on prandial insulin. And so, simplifying her regimen, which means actually U-500 because that will be either 2 or 3 shots a day, would actually, potentially, be a real relief to her because then she doesn't have to

give quite so many injections.

Dr. Russell:

So, if I've got her at over 200 units a day and I'm not anywhere near my A1c target, how would you go about switching her from my basal bolus regimen to the U-500?

Dr. Peters:

So, I take the total daily insulin dose. So, let's just pick a number for her. We'll say 220, and I would start her on a twice-a-day U-500 regimen just because twice a day is easier than 3 times a day. Now, arguably, 3 times a day may be the best in terms of the pharmacokinetic profile, and she may end up on 3 times a day, but if you ask people the dose they miss the most, at least in my practice, is that before-lunch dose. I think when people are out and about, living their life, they often forget that dose.

So, I would take her total daily dose, and I would give her 60% as U-500 before breakfast and 40% as U-500 before dinner, and I would then stop the other insulins and keep her on metformin because I think that's a good drug no matter what.

Dr. Russell:

So, for our colleagues who aren't real comfortable and don't really know a whole lot about U-500, could you explain its pharmacokinetics?

Dr. Peters:

Well, even to us in the field, U-500 is kind of a mystery, but it's an extra concentrated insulin, and it's like a combination of a regular insulin and a long-acting insulin all at once, and so, if you give it, it doesn't start working fast like rapid-acting insulin, like lispro or aspart, but it starts acting more slowly—but that's okay, because these people are relatively slowly absorbing their food anyway—and then you basically get a longer tail. So, the tail can last up to 24 hours. So, in a way, it's both a prandial and a basal insulin. In terms of adjusting, I'd want for sure her fasting, because her fasting sugar basically controls the dose you're giving before dinner. So, if her fasting sugar is still high, you're going to increase the dose before dinner, and I do it in around 10% increases, but it really depends on what people are comfortable with, but generally, I'll increase it in 2 units, 4 units, just depending on how I think she's responding. A lot of this is getting a feel for the patient. Some patients are terrified of hypoglycemia at night, so then I might only go up by 2 units each time until her fasting comes down to what I want. And then, I would adjust the morning dose based on what her before dinner blood sugar is. So, I would really use those 2 values, the before breakfast and the before dinner, to be adjusting. But if you start seeing that no matter what you're doing with that morning dose isn't working, then I would check some before lunchtime and maybe then split it and then give her before lunch U-500 as well. So, you need to get a sense if that morning dose can control the entire day or if you need to add a third dose.

Dr. Russell:

You mentioned hypoglycemia. What's the data on hypoglycemia with U-500?

Dr. Peters:

Well, I personally think it's about the same as with any other insulin, because it's insulin, and insulin all causes hypoglycemia. The good news is, in our type 2s the rates of hypoglycemia, particularly severe hypoglycemia, are much, much, much lower than in people with type 1 diabetes. So, I think that we need to make sure patients are prepared to understand what the signs and symptoms of hypoglycemia are, how to treat hypoglycemia, just the general education.

Dr. Russell:

So, in talking to Justine, how would I tell her that U-500 comes? How is it supplied for her to take?

Dr. Peters:

Well, these days we have U-500 pens, actual insulin pens that are U-500, and we also have U-500 syringes. So, in the past we used to really struggle with whether it's syringe units and this, that and the other thing, but now with the pens and the syringes, you just give her the dose, so you take... Say you wanted her on 500 units of insulin. You just say 10 units. You'd give it as the dose would be in the pen, that it's easy for the patient. It becomes seamless.

Dr. Russell:

Any other practical tips on using U-500 for primary care doctors who want to kind of start doing this for their insulin-resistant patients?

Dr. Peters:

I think the biggest problem with any insulin is titration. So, I think all of us are pretty good at initiation, but you asked earlier, when do you follow her? And I personally think when I start a patient on insulin that I need some sort of weekly followup because I want to see how they are doing. So, I think we can get her down together and then check her A1c in 3 months. And, you know, you're probably not going to get her below 7, but if she gets a 1% reduction in A1c, you're going to be ecstatic. And, at the same time, this is insulin, and insulin can cause weight gain, so I would have her work with a dietitian. I would encourage exercise. In these incredibly insulin-resistant

patients, exercise is like magic, right?

Dr. Russell:

So, Dr. Peters, you mentioned hypoglycemia, and that transitions great into the next case I'd like to discuss with you. So, for Justine, we talked about her insulin growing to over 200 units a day, and we decided to switch her to U-500 because of the volume. But my second patient, Carl, is an obese, 62-year-old male who has an 8-year history of type 2 diabetes. He has some cardiovascular disease. He's on metformin, he's on empagliflozin, and he's on liraglutide, and he takes 60 units of U-100 glargine at night. But over the last couple months, he's had 1 to 2 episodes of nocturnal hypoglycemia each week. On his most recent fasting blood glucose, he's running 110 to 135, and his A1c is 7.2. You know, this hypoglycemia clearly has him worried, clearly has me worried, and I've heard that some of the pharmacokinetics of some of the newer more concentrated insulin can help with that.

So, in your opinion, where should I go with this issue mainly being nocturnal hypoglycemia in someone who's not that far from goal, who's at 7.2? So, would you use a U-300 or a U-200 degludec?

Dr. Peters:

Well, so, this is a classic case, and I want to tell you that you've done a great job with him. Right?

Dr. Russell:

Mm-hmm.

Dr. Peters:

You have him on empagliflozin, and you have him on liraglutide, which are both drugs that help reduce cardiovascular risk and death in a patient with known cardiovascular disease, so that's great. So, the first thing I do here is I set my A1c target. So, he's 62, which in my world isn't old, but on the other hand, he has cardiovascular disease, so I would say that my target A1c for him is somewhere between 7 and 7.5. Right?

Dr. Russell:

Right.

Dr. Peters:

You don't need him down below 7 because you're going to cause lows. So, he's already at target, but he's at target with nocturnal hypoglycemia. And we know that severe hypoglycemia increases your risk for overall cardiovascular mortality, so we don't want to hurt him while we're trying to help him. So, the deal is, is that the 2 insulins you discussed, U-200 degludec and U-300 glargine, are both long-acting insulins with a reduced risk for hypoglycemia, and I would definitely switch him to one of those two.

Dr. Russell:

So, how do I discern between these 2 insulins?

Dr. Peters:

Well, they are somewhat different in how they are made and in how they work. So, let me talk about degludec, which is sort of the easier to differentiate. It's the longest acting insulin we have. It lasts for up to 42 hours. And one of the nice things about it is you can not only give it at any time of day, you can also miss a dose and it's still there at a high enough level in your body. But it's a very slow insulin, so I tell people, instead of adjusting it every day, you need to adjust it every 3 days, because it's so long-acting, but it's associated... In every study they compared to U-100 glargine but with a significant reduction in rates of both mild and severe hypoglycemia, and in their big cardiovascular outcomes trial comparing it to U-100 glargine, there was a lot less hypoglycemia—in particular, less nocturnal hypoglycemia. So, degludec—and there's the U-200 degludec, which is a pen where it's more concentrated—it's not any different than the U-100 pen. It's just that it has 160 units in a pen instead of the smaller number that's in the typical pen.

The U-300 glargine also is associated with less nocturnal hypoglycemia. It's a more concentrated form of U-100 glargine. And again, it's got this nice profile that at night there's less hypoglycemia. It's not that 42-hour length of action. It basically is more similar to the length of action of the U-100 glargine, but it doesn't peak. So, U-100 glargine has sort of a peak at about 12 hours, a small peak, but in some people that's more pronounced, and the U-300 is flatter, and if you look at the data on it, it's just a flatter basal and it causes less hypoglycemia.

Dr. Russell:

So, overall, clarifying, you would keep their doses the same. You would just kind of think about something that's going to protect him from some of those hypoglycemias. Is that correct?

Dr. Peters:

Well, yes, but there's a subtle point.

Dr. Russell:

Okay.

Dr. Peters:

So, U-300 glargine is actually the one that you have to give the most of, so there's always a couple units more to reach the same target. So, if he's on 60 units of U-100, he's going to end up on 63 or 64 of the U-300, and if he's on 60 of the U-100, he's going to need less of the degludec, so I always basically decrease if I'm on... If I have a patient like this patient, I would probably start with 56 units of the degludec, and I would start with 60 of the U-300 just because I can up titrate easily. I don't want to overdose when I start. But, in general, U-300 will be a little bit more than U-100, and U-200 degludec will be a bit less.

Dr. Russell:

So, Dr. Peters, do you have any final pearls for someone like myself who's a primary care doctor about looking at kind of newer insulins when they come out?

Dr. Peters:

I think that you need to look at what the goal is, and I think it's really, actually, simple—is that if your goal is to treat somebody on more than 200 units of insulin a day, then using U-500 makes sense. And that's sort of me to just like adjusting any insulin, because it seems magical, but it isn't. It's just the insulin dose you're used to.

With the other insulins, with U-300 glargine and U-200 degludec—which, by the way, is the same as U-100 degludec, again different from the pen—but degludec and the U-300 glargine are very long-acting insulins for patients where they are developing hypoglycemia on a more traditional basal, such as NPH or U-100 glargine. So, one's more about hypoglycemia and duration of action, and one's about high doses of insulin. So, in a way, it's simple, and it's wonderful to me as a diabetologist because I now have these choices. Right?

Dr. Russell:

Well, Dr. Peters, thank you so much for helping me out with Carl and Justine, my 2 patients, and helping demystify these new concentrated insulins. Thank you.

Dr. Peters:

Great, thank you.

Narrator:

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