

Seven Things to Know About Treating Hyponatremia



PODCAST 2

Dr. Jill Sellers:

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Dr. Jill Sellers:

Our guest today is Dr. Biff Palmer. Dr. Palmer is a distinguished Teaching Professor of Internal Medicine at UT Southwestern Medical Center in Dallas, Texas. He received his medical degree from UT Southwestern Medical School, completed a residency in internal medicine and a research fellowship in the Department of Nephrology at Walter Reed Army Medical Center in Washington, D.C., and a clinical fellowship in the Division of Nephrology at UT Southwestern Medical Center, Parkland Memorial hospital. Dr. Palmer is board certified in internal medicine and nephrology. I will provide a link to his full bio in the show notes. Welcome Dr. Palmer.

Dr. Biff Palmer:

Well, I'm very happy to be here and I thank you for this opportunity.

Dr. Jill Sellers:

Well, I'm glad you could join us today. You and I have actually worked on a previous medical education project for the European Society of Cardiology meeting in Barcelona, Spain. And I'm not sure if you remember, but I remember dining with you at the Etapes Restaurant and learning about your mountain climbing adventures. And for our listeners, Dr. Palmer is a member of the Seven Summits Club and he has a TED talk that I will also link to in the show notes that I highly recommend you watch. It is excellent. And for those of you who may not know what the Seven Summits Club is about, I'll let Dr. Palmer explain it and how he got into mountain climbing.

Dr. Biff Palmer:

Well, thank you for sharing that experience. The Seven Summits are considered to be the tallest mountains on each of the continents. I was very fortunate to be able to climb these. The way I got interested in it is somewhat unusual. I did not start climbing until I was in my mid-40s. And I just really became kind of fascinated with these documentaries, like on *National Geographic* or the Discovery Channel about these expeditions. I just thought it would be interesting to try it. And as I really detailed in some of those lectures that you mentioned, like the TED talk, my initial foray was quite disappointing. I tell the story about how I basically tried to get into shape and then ultimately was able to have a successful summit of each of those mountains. I really appreciate you telling the audience about that project.

Dr. Jill Sellers:

Well, it is quite an accomplishment, and I don't know how many people have done that.

Dr. Biff Palmer:

Oh. No, I don't have an exact number. I mean, more and more people are doing it, but it's still a pretty exclusive club, at least I'd like to think.

Dr. Jill Sellers:

Well, I imagine throughout all this mountain climbing that your nutrition and hydration is extremely important, especially during a multi-day climb. And speaking of hydration, let's jump into our discussion on hyponatremia. For purposes of laying the foundation for this podcast, I'd like you to describe for our listeners what hyponatremia is and how it is diagnosed.

Dr. Biff Palmer:

Hyponatremia, or a low serum sodium concentration, is really one of the most common electrolyte disturbances that clinicians find either in the outpatient or the inpatient setting. And what hyponatremia really represents in virtually all cases is that relative to the total body sodium content, there's an increase in total body water. And that's somewhat of a hard thing to bring about because your normal functioning kidney has a tremendous capacity to get rid of excess water. So for hyponatremia to develop, there has to really be some impairment in your kidneys' ability to excrete ingested water.

Dr. Jill Sellers:

So it's not necessarily an intake issue, it's more of an organ function issue?

Dr. Biff Palmer:

Well, in order for it to develop, there certainly has to be water added to the body. But the point is, under most circumstances, your kidney will be able to recognize the water intake and quickly reestablish water balance within the body. But there are circumstances, particularly those circumstances that cause an increase in the blood level of vasopressin, that in turn leads to a defect, if you will, or an impairment in the normal kidneys' ability to excrete water.

Dr. Jill Sellers:

Is hyponatremia something that is commonly overlooked by healthcare providers?

Dr. Biff Palmer:

Well, it's a fairly common diagnosis and actually an easy one to make because the basic metabolic profile, which is a chemistry test that virtually all clinicians order, whether you're in a primary care setting or a subspecialty setting—it encompasses all the electrolytes. Where hyponatremia is discovered is oftentimes just on a routine, basic metabolic profile test. So where clinicians have difficulty is when it's discovered and what exactly should you do? What are the considerations to be sure there may be some individuals who have some or mild symptoms and even non-specific symptoms, things like a headache, or just not feeling well, fatigue, what have you, that you get a basic metabolic profile and all of a sudden you discover hyponatremia. So I think it's an easy diagnosis to make because the tests that we order are quite common. I think where clinicians though find a great deal of difficulty is how best to approach treating it.

Dr. Jill Sellers:

Okay. So when does one decide to treat hyponatremia? And subsequently, are there specific patient types that are more prone to it?

Dr. Biff Palmer:

Yeah. So, that's a great question. In general, like I say, hyponatremia represents a state where there's an increase in circulating vasopressin. I think what clinicians and the podcast audience needs to remember is that there's really only two categories in which vasopressin becomes higher than normal. Perhaps the most common one is when there's some circulatory disturbance—what I mean by that is an underfilling in the circulation. When that occurs, pressure sensing mechanisms that are widely distributed through the body, because of that underfilling, and that then mediates the release of vasopressin. That's one main category.

The other category is where vasopressin is high within the blood, but yet the circulation in the body is absolutely normal. When that occurs, we usually use the term syndrome of inappropriate antidiuretic hormone secretion. Again, that's kind of a broad term, but it is meant to encompass patients who may be on some centrally acting drug that's causing stimulation of its release, it may be people who have a tumor that is autonomously secrete vasopressin, but the point is the SIADH patients have an absolutely normal circulation. So the two main categories are circulatory underfilling and a normal circulation where the secretion is more autonomous.

Dr. Jill Sellers:

Okay. And then in treating it, then how do you decide when to treat it?

Dr. Biff Palmer:

The treatment, again, is for everybody who has a low sodium. You first of all, need to discover why it has come about and then to do the best that you can to try and remove the underlying cause. I think an attempt should be made to treat all individuals, if you are able to, I mean, there are some certain conditions where, for example, you can't really remove the underlying cause. Some of the maneuvers then that one would employ would be free water restriction. But I think most clinicians would agree that telling somebody to restrict free water intake has a very variable effect, and it's oftentimes difficult to enforce. If there's a problem in the circulation, and you can correct that problem, for example, maximizing somebody who has impaired cardiac function or somebody who happens to be salt depleted and administering saline, those are readily effective maneuvers that can be utilized. It is really patient specific, but to summarize, it's very important to try to identify the cause of the hyponatremia and then whenever possible, institute the appropriate therapy.

Dr. Jill Sellers:

Which makes perfect sense to me. So how important would a proven day one response of serum sodium with intravenous conivaptan be in patients admitted to the ICU? And how would you administer it?

Dr. Biff Palmer:

Conivaptan is a drug that blocks the receptor in which vasopressin acts. That receptor is located on the terminal part of the nephron. And when vasopressin interacts with that receptor, it causes the insertion of water channels. That then provides a mechanism for water reabsorption and the maintenance of hyponatremia. Conivaptan represents a receptor blocking agent that sometimes people generically call

“vaptans”. So what conivaptan does is block that receptor so vasopressin no longer causes insertion of those water channels into that nephron segment. And therefore, water will now be promptly excreted by the kidney and the excess total body water will be corrected. Again, where we would tend to use this drug would be in individuals who have SIDH or people who have circulatory disturbances like heart failure or cirrhosis. In other words, circulatory disturbances that are not readily fixable by just simply giving somebody saline. The clinical trials with this particular drug have shown that it is very effective within a 24-hour period. And really within several hours, you start to see a demonstrable increase in your serum sodium concentration. So again, it is a very effective therapy and it works as you phrase it even within the first 24 hours and I would argue even within the first several hours of administration.

Dr. Jill Sellers:

Excellent. I mean, that's very good because these are usually patients that need to have it working sooner rather than later. To me, that's probably one of the ways this particular drug has changed the way hyponatremia is managed. Or how has it? I mean, how has it changed how hyponatremia is managed?

Dr. Biff Palmer:

Well, I think it's been a welcome addition to the armamentarium. When you again, think about hyponatremia in an intensive care unit setting, these types of patients almost by necessity are being given large quantities of various fluids because they require antibiotic therapy, they may require pressure support, for example. I mean, anytime you visited an ICU, you will always note multiple intravenous infusions in the most common scenarios. So, you're really dealing then with a situation where water intake cannot be readily restricted because by necessity, you're having to give fluids to allow these medications to be administered. And this again provides now a nice means to help correct that problem because by giving a drug that's limiting the kidney's ability to excrete that water load, you now can more effectively manage the excess water that oftentimes develops in these ICU individuals.

Dr. Jill Sellers:

Tell us about the challenges and successes of using conivaptan in your practice.

Dr. Biff Palmer:

Yeah. I've already kind of alluded to some of the successes. And what I have found again in the ICU setting is that these individuals who are given large amounts of free water, we can now, by using this agent, really allow people to establish a more neutral water balance. In other words, not always be in a positive water balance. The big challenge of course is that it is an intravenous medication, so it does require IV access. You can utilize a peripheral line. One of the well-known side effects of the drug though, is it can cause a phlebitis kind of an inflammation of the vein in which its being infused into and so on occasion, you have to rotate the sites because of this localized inflammatory change. This inflammation is thought to be due to the diluent more so than the active drug, but nevertheless it's a complication to be aware of, yet easily overcome.

Dr. Biff Palmer:

The other thing I would just mention is that when using this drug and frankly, in anybody with hyponatremia, you always have to monitor the patients closely to make sure that the rate at which you correct the hypernatremia is not excessive. In individuals in which hyponatremia has been present for 48 hours or less, we try to keep the amount of correction, right in the range of 6-8 milliequivalent in any 24-hour period,

because more rapid correction increases the risk of what has been called osmotic demyelination. So that's one of the challenges that one must keep in mind when using this or really any approach to treating a chronically hypernatremic subject.

Dr. Jill Sellers:

What advice would you give to colleagues who are considering the use of conivaptan?

Dr. Biff Palmer:

We need to keep in mind that it's part of the armamentarium. When we utilize the drug it is oftentimes, and most commonly, given as an initial bolus of 20 milligrams administered intravenously over a 30 minute period. Then you can follow that up with a continuous infusion of 20 milligrams over 24 hours for up to four days. The regimen that I just described was the way it was administered in the trials that ultimately led to the drug being approved. So again, 30 minute infusion, almost a loading dose, followed by a continuous infusion up to a four days. Now having said that, interestingly in post-marketing use of this drug, there have been well-described instances where people have simply given the loading dose of 20 milligrams administered over 30, just on separate days. In other words, titrate intermittent dosing according to the response that was achieved. You see this a lot in the neurosurgical literature, yet again, it's an off-label administration, at least when you look at the packaging for this particular product.

Dr. Jill Sellers:

Interesting. I'm going to switch gears here a little bit. We've gotten through, I think what's the worst of the pandemic with COVID-19 and I'm just curious what, or if you can tell us anything about the incidents of hyponatremia in COVID-19 patients.

Dr. Biff Palmer:

Yeah, that's obviously a very timely question. There have now been numerous papers describing the clinical experience with these individuals, particularly in the ICU. And again, supporting the idea that first, hyponatremia is common and it's quite likely common because once again, these individuals are frequently given large quantities of IV fluids for the treatment of the virus itself, but also the various comorbidities that accompany the virus. So again, water intake is quite large with these individuals. The other thing to keep in mind is the COVID 19 infection is very much localized to the lung parenchyma and it's well-known that almost any kind of infiltration into the interstices of the lung can lead to increased vasopressin release.

So again, just through these mechanisms, you can understand then why hyponatremia would be a common entity. In some of these papers, the hyponatremia in this setting has been associated with increased morbidity and mortality in these individuals. I think it tells us that there is a need to be cognizant for this electrolyte disturbance developing and to also be somewhat aggressive in trying to not only prevent it, but actively treat it. And again, this fits in line with our discussion of the use of this particular vaptan, conivaptan.

Dr. Jill Sellers:

So, that was going to be my next question. What is the procedure or protocol for treating these hyponatremic COVID-19 patients? Is it different? Does conivaptan have a place here? And is that different than how you would treat other hyponatremic patients knowing that this is a lung infection and that it can increase the ADH and all the other things that come with that?

Dr. Biff Palmer:

Yeah, so I think it's very similar to really anybody who has hyponatremia. Again, I think that given the association, and it doesn't prove causality don't get me wrong, but the association with worse outcomes, or higher amounts of morbidity, again, provide at least a justification for early treatment of the disorder. So again, if somebody started to drop their serum sodium to less than 135, and certainly down to 130, I would immediately begin to try to understand why is this developing? Are there any quick fixes? Is there some sort of an IV fluid that I could cut back on? I don't want to minimize that as an important aspect. One certainly must look at the IV intake. And are there ways that one could limit the amount of free water intake? But again, you're oftentimes hamstrung on how much water intake you can limit because of the necessity for the various medications to be administered.

I think this fits nicely into the use of these vaptans because we know by antagonizing the effect of the vasopressin at the level of the kidney, it allows for increase water excretion by the kidney. I would point out that this drug and this whole class of agents, the vaptans, they're only going to work if you have reasonably good kidney function. As people develop progressive acute kidney injury, which is certainly common in this infection, then the effectiveness of a vaptan is going to be much less. If kidney function is reasonably well preserved, then the drug should work reasonably effective. And again, as I say, is a welcome armamentarium to our therapeutic strategies.

Dr. Jill Sellers:

And have you treated COVID-19 patients who are hyponatremic; who have poor kidney function?

Dr. Biff Palmer:

There's no specific toxicity of the drug when administered in somebody who has impaired kidney function, and there's no dose adjustment that needs to be utilized. But you do have to be prepared to see much less of a response. In other words, when the glomerular filtration rate is markedly reduced, let's say because of acute tubular necrosis, interstitial nephritis, or whatever may be the cause, vasopressin really is no longer an issue at that point. The hyponatremia is largely developing because the water intake is simply greater than the small amount of surface area that is left or filtration of fluids. Just to summarize, you don't need to adjust the dose, you just need to be prepared for much less effectiveness as the glomerular filtration rate falls to let's say 30 milliliters and below.

Dr. Jill Sellers:

Can you comment on the utilization of conivaptan among your nephrologist colleagues? And what has been the discussion over its use? And this doesn't necessarily have to be in COVID-19 patients, just in general, overall.

Dr. Biff Palmer:

I think many of my colleagues have started to embrace the use of the drug over the last several years. And again, perhaps this pandemic has really brought out the utilization. I get the impression at least, and I can't provide you any hard data, but I think the utilization of this drug has increased in the course of this pandemic because of the large burden imposed in ICU patients. Where again, as I say, you're faced with this dilemma, a lot of fluids coming in and overwhelming the kidneys to excrete it because the COVID-19 and all of the comorbidities are stimulating vasopressin. I say, COVID-19 is stimulating, there's actually evidence that the cytokine storm that's been associated with this infection, particularly some of the interleukins, can

actually centrally stimulate vasopressin release. It's kind of an interesting connection there. So yes, I think we'd been utilizing the drug more. And as I say, I've been finding reasonably good efficacy as long as the kidney function is reasonable as I've previously commented on.

Dr. Jill Sellers:

When the pandemic hit, how did that affect your practice? And are things getting back to normal now? Or do you think it will be a while longer?

Dr. Biff Palmer:

Yeah, I mean, that's a great question. And there is absolutely no question, at least here in my area where I live in Dallas in the various teaching hospitals that I work at, the numbers of patients have clearly gone down. And the number of people who are admitted in the ICU is strikingly improved. So hopefully that will remain the case. I mean, it's concerning that, for example, we read about these surges in countries like India and in Brazil, whether or not that's related to these variants, who knows. I do think we'll have to be vigilant to make sure that we don't start to see that here in the United States. But certainly in my area, the country, we're definitely on the proper end of the curve at this point.

Dr. Jill Sellers:

So Dr. Palmer, before we close, what are some final thoughts that you'd like to reinforce with our listeners regarding hyponatremia and its treatment?

Dr. Biff Palmer:

Well, there's absolutely no question. I would say number one, hyponatremia is arguably the most common electrolyte disturbance that one finds on a basic metabolic profile. And unfortunately, many clinicians find it very intimidating. But I think you can make it much less intimidating, if number two, you realize that hyponatremia simply represents water intake in excess of what your kidney can excrete. The third main point is that when there is some evidence that your kidney is not excreting appropriately, the water that has been administered, it generally means there's excess vasopressin. And the fourth point is that when vasopressin is high, there's really only two reasons for it to be elevated. One is that there's some derangement in the circulation, such that the body is sensing there is underfilling. The second component is when the circulation is normal, but vasopressin is high and we'll utilize the term SIDH.

A fifth point is that when we initiate or begin to think about treating the disorder, we obviously want to pay a great deal of attention to the rate at which it's being corrected. Again, in hyponatremia that's been present for more than 48 hours, you want to make sure that you raise the sodium by any more than 6-8 milliequivalent in any 24-hour period. Number six, I would say that the vaptan class, of which conivaptan is a member, binds to the V2 receptor in the distal part of the nephron and antagonizes and prevents vasopressin from causing water channel insertion. In this sense, the drug is very physiologic. It's a physiologic way to approach this defect in kidney water excretion. The last point I'd like the audience to remember is that there's absolutely no question that I think conivaptan and the ability to block this V2 receptor is a tremendous addition to our therapeutic armamentarium to treat this very common electrolyte disorder.

Dr. Jill Sellers:

Thank you. This has been excellent. Thank you, Dr. Palmer for being part of the *On Medical Grounds* podcast and educating us on conivaptan and its important role in hyponatremia management. It has been great. Thank you very much.

Dr. Biff Palmer:

Well, thank you very much for having me, and it's been a true pleasure to talk about this subject that I think clinicians face every day on a clinical practice basis.

Dr. Jill Sellers:

And thank you for listening to the *On Medical Grounds* podcast instructions for processing your continuing medical education credits and the resources that were referred to in this podcast can be found at onmedicalgrounds.com. In addition, please be sure to click the subscribe button to be alerted when we post new content.