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https://reachmd.com/programs/cme/case-management-strategies-for-patients-with-adpkd-part-2/13880/

Released: 01/31/2023
Valid until: 01/31/2024
Time needed to complete: 30 minutes

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Case Management Strategies for Patients with ADPKD – Part 2

Announcer:
Welcome to CME on ReachMD. This activity entitled "Case Management Strategies for Patients with ADPKD, Part 2," is jointly provided by Novus Medical Education and Medical Education Resources. And this activity is supported by independent educational grants from Otsuka America Pharmaceutical Incorporated.

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Dr. Rahbari-Oskoui:
Hello, and welcome to the webcast titled “Optimizing the Care for Patients with ADPKD. This is based on Case Management Strategies, Part 2.” I'm Fred Rahbari. I'm a Professor of Medicine at Emory University in Atlanta. And we're going to review several common patient cases and provide insight into practical evidence base and standard care management strategies to help achieve optimal care for patients with ADPKD.

Before we get started, let's review the learning objectives. And the first one is to discuss standard of care strategies to manage chronic kidney pain in patients with ADPKD. Second one is to mitigate excessive polyuria in patients with ADPKD who are treated with tolvaptan. And the third one is to summarize strategies for managing transaminitis in patients with ADPKD who are treated with tolvaptan.

We'll start with the case number one that I call, ‘a painful journey.’ So this is a 40-year-old lady with PKD and uncontrolled hypertension since the age of 18, preeclampsia, mitral valve prolapse, headaches, and dyslipidemia. And I got to know this patient around age of 40. And from the point of our first contact, she was complaining about flank pain, and had a couple of episodes of UTIs over a year and a half, typically to E. coli treated by antibiotics, macrolides. And the level of pain was increasingly going up over the years. And the first beginning years, she was well controlled on just Tylenol, heat pads and mostly at night. And also we had to apply for work accommodations for her not to have to lift children because she was a school teacher and also giving her some time to have extra stretching at school so her kidneys would not hurt as much. But with time, narcotics are started with dose escalation and the pain was increasingly disabling her to be comfortable and do her work and also in her sleep.

So by the time that she was about 42 of age, we got to the point that I approached her for interventional strategies of maybe cyst deroofing or cyst aspiration. And we did the MRI of her kidneys and, as you can see on the images, so the top images are all T2 acquisitions sequences. The top parts are coronal images, and the bottom two pictures are the axial pictures. And you can see that there are several cysts on each kidney that are lighting up in white and T2 acquisition image and there were multiple of them. And her pain was mostly in the back. When we did the - at the age of 42, when we did the CAT scan to decide to do the cyst aspiration, which is - which was finally her choice, it was very obvious that area that she was hurting was primarily on the right side with a major prominent cyst. And when we did the cyst aspiration on that site, literally on the table, she had a major dramatic improvement in her level of pain. And she was very happy with the results. So this was in March.

She comes back about 3-4 months later complaining of contralateral pain. Again, you know, the area of the pain was predominant cysts

on the left side this time, and we decided to go for left cyst exasperation with a doxycycline injection after that. And again, very quickly and dramatically, she improved with her pain level right after the procedure. This goes on for a few months.

And now we're in September – I mean December, so about, you know, 6 months later than the previous procedure. And at this point, her pain was, again, more predominant on the left side, and we said, 'we're going to go and do another procedure.' She underwent the procedure. And what happened right after that, within 30 minutes, she started having shortness of breath, hypotension, tachycardia, and the chest x-ray showed major left-sided hemothorax that you can actually see on the chest x-ray on the left side. And the CT was clearly showing that there's a large hemothorax on the on the left side.

And one week after that, she was - obviously she was put in the ICU and was under care. And originally, we didn't want to touch that large amount of blood that was sitting in her left lung, and because we were worried about the bleeding resuming again. But within a week, unfortunately, she went to the point of collapsing her lung and needing CT surgery and basically taking all the clots out of the left lung. And finally after that, she did well that thankfully, and her dramatic episode there result within a couple of months without the sequelae.

The natural history of this lady was that over the following 4 years, the pain continued to take a toll on her daily life. Repeated imaging studies showed that the aspirated cysts have come back. And because of the dramatic complication that she had before, she decided not to pursue any other procedures and the pain management was moved from short-acting narcotics to long-acting narcotics such as oxycodone, - I'm sorry, OxyContin - from hydrocodone to OxyContin. And this was helping her as far as the pain and also her blood pressure was going up and she was in a lot of pain. So the blood pressure also improved.

And over the following 11 years, by age of 51, she underwent a kidney transplant. And the negative kidneys were removed couple years later, after she had received her transplant.

So, this is a very interesting, fairly typical for the beginning of the presentation, but atypical in the complication that she had majorly at the third cyst aspiration. And the pain management strategies that this patient went through - actually she went - she used several of these strategies along the years. And the problem with kidney cyst size and pain is that the correlation even though it exists, is not perfect. So there are people who have very large cysts and not a lot of pain, and other people have small cysts and they have a lot of pain.

So if you see that somebody has an, what I call an overall pain syndrome, if they have IBS, irritable bowel syndrome, fibromyalgia, chronic nonspecific body aches, hypochondria, conversion disorders, if you see that set up, I do not usually recommend a procedure. Because just by doing a procedure, you're increasing their nociceptive signals and that basically increases the level of pain without really taking care of the kidney pain. And if you always try to start with non-invasive, non-pharmacological strategies, ice, massages, heat padding, Whirlpool, and the Alexander Technique which is basically how you position your body to reduce the amount of pain on your kidneys when you're sitting and you're moving around. And also sometimes psychological behavioral modifications can be used.

Then the next slide would be typically non-opioid medications. And Tylenol is the safest for the kidneys, and say then salicylates have been used, but we know that they can cause kidney dysfunction in some patients and COX-2 inhibitors in the same level. Tramadol, clonidine also have been used, although clonidine has a notorious side effect of brain fog or risk of hypotension if patients are not hypertensive.

And then we move to opioid management. And obviously the major issue there is the risk of dependence and tolerance. They're short acting. The long-acting opioids, and you can use adjuvant strategies such as gabapentin, amitriptyline, pregabalin for enhancement of the pain management.

Then we move into intervention-based procedures. Acupuncture has been used, transcutaneous electrical nerve stimulation has been used in PKD. Spinal cord stimulation with neuromodulation has been used. And then neuraxial opioid and local anesthetics, celiac nerve - plexus nerve block that has been more recently used are effective in patients who have very chronic and severe pain. As far as the cyst aspiration, the criteria are relatively fairly robust. If you take exactly like this patient, and somebody who has predominant cysts exactly where they hurt. If they point out with a finger that my back is hurting, and right there, there's a large cyst that is usually 3 to 4 centimeters large at least, then your success rate is very high, and if they don't have that subset of pain syndrome. Otherwise, if all the cysts look the same and the pain is diffuse, you will not be successful in controlling the pain.

And then more advanced is decortication marsupialization, cyst deroofing, those are more complex surgical laparoscopic typically surgeries. And sometimes you may have a non-healing wound that would be oozing fluid.

And then ultimate treatments are innervation or nephrectomy that we typically really take to the last, last chance.

So this case basically summarizes almost half of the strategies for pain in one single patient, for pain management. It's a very illustrative

case for these patients.

Case two, moving along, is a case of polyurea on tolvaptan. And we call it is, 'how bad can it get.' This is a real-world case, a 35-year-old Caucasian male was very tall, 6 foot tall, weighing 280 pounds, and has hypertension and PKD and treated with one single medication, lisinopril. And he comes in, we start tolvaptan, and with increasing doses. At the first dose of 45 plus 50 milligrams, the urine output was about 6 liters. At the middle dose of 60 plus 30, we were basically dose titrating urine output to was up to 7.5 liters. And by the time we were at the maximum dose, at 90 and 30, urine output was about 10 liters. Also along that way, his blood pressure started going up by about 8 to 9 points millimeter of mercury, reaching about 135 at over 85. And this is unusual for this patient. He's also a CEO of a company and now he has to go to the bathroom pretty much every 45 minutes to an hour or, so he had to cut back on his meeting time to less than 45 minutes. Creatinine was relatively stable during this time, from 1.3 to 1.4, which was not a major significant rise. And we were happy with the kidney function.

So the question becomes what do you do with somebody who was urinating 10 liters a day, that is usually if you're at that point is almost going to the bathroom somewhere between 16 to 20 times a day. So this is really excessive. To get back to the data that was generated during the phase 1 trial of the tolvaptan, you can see on this image, the study was basically just a single oral dose and they were trying to see what the maximum urine output is over 24 hours. And you can see that with increased those from 50 milligrams to 120 milligrams single dose, the urine output when from 5 to 10 liters. Again, this is just one single drug - one single dose of the drug.

And then we had 5 days of chronic use of tolvaptan. And you can see that in that case, the amount of urine output is actually less and it plateaus around 6 liters even at the highest dose. So there's basically an effect that the urine output attenuates a little bit from the maximum of one dose. And this is very important to kind of remember that what - this is what could happen. And this patient was really at the very, very high end of the response.

So, to put this in perspective, the polyuria counts for about 15% of all patients who are dropping out from tolvaptan. And also, it can disrupt sleep pattern, it can cause worsening of hypertension. The strategies that have come by over the last several years to mitigate and improve this excessive urine output are, obviously, number one, if there are the highest dose of tolvaptan, you can go on a lower dose, recheck the urine osmolality. If they're still maximally diluting the urine at least to urine osmolality of less than 250, ideally even lower than that, then you can kind of say we will get the same benefit in keeping them on a lower dose.

If you're already on the lowest dose and you still have an excessive urine output, then you can complete a 24-hour urine and see what their sodium excretion is, which is basically a reflection of how much salt they eat. If their salt intake is excessive, you educate them about limiting their salt intake.

And then more recently, hydrochlorothiazide has been suggested to be added to this regimen. So the effect of hydrochlorothiazide was formally assessed by the Dutch group. And they basically designed a trial of hydrochlorothiazide and metformin and placebos at three arms. And the patients were also on tolvaptan on the hydrochlorothiazide and metformin arms. And as you can see, the amount of urine output was decreased in the group that was on hydrochlorothiazide compared to placebo. Placebo was 6.34 liters, hydrochlorothiazide 5.13 liters. And as a consequence, also the GFR was slightly lower in the hydrochlorothiazide group 51 versus 55 in average. But plasma copeptin, which is an indirect marker of vasopressin levels, is actually - was also lower in the hydrochlorothiazide group compared to placebo. And that basically shows that vasopressin is adequately suppressed in that case. So you could potentially use this strategy to mitigate the excessive urine output and make patients more comfortable so they can stay on the drug and get the benefit.

The last cases are actually two cases in one and I put them side by side to kind of compare what's different and what is the difference in strategy. The first case is a 43-year-old male with PKD started on tolvaptan 4 weeks ago. And as you know what the REMS requirement, you have to do liver function test at 2 weeks, and then every 4 weeks. And he's up to 60 and 30, goes to a party over the weekend has 6 beers, and then shows up to the lab on Monday for his 4-week checkup. And the LFTs that were originally normal or now AST is up to 120, ALT up to 130. Right under that, times three normal cutoff but bilirubin and alkaline phosphatase are normal.

The second case is almost a male of same age, 45 years. But this one has been on tolvaptan 60 and 30 for 4 years without any major issues at all whatsoever. And liver function tests were all normal. And comes to a regular follow-up visit and all of a sudden AST is up to 150, ALT is up to 140. So now we have at least more than three times increase in transaminases, but bilirubin and alkaline phosphatase are still normal. He denies any alcoholic intake, has been on atorvastatin for 4 years, no dose change. But his primary care just recently added fenofibrate to his regimen, so that's the only difference here.

So what do we do in this case is the question is basically relevant to - the questions are irrelevant in both cases. Either we stop tolvaptan immediately, continue tolvaptan and ask the patient to go to a lab, and then avoid, obviously, alcohol intake and repeat LFTs in 3 days and see whether they're going up or not, or option C would be to admit the patient to a liver transplant center for pending hepatic failure or admit the patient to the ICU for what we call MARS therapy, or molecular adsorbent recirculating system, or also called liver

dialysis.

The answer to this question - so in the in the first case, so if you have a patient who's still under the three times normal limit have increased, but it happened very quickly. But there was also alcohol intake. So we sent him back to the lab, and 3 days later, an AST is up to 180 and ALT is up to 160. At that point, again, bilirubin was still normal, so the trigger is to stop tolvaptan at that point, and repeat AST and ALT and bilirubin regularly over the - I did almost twice a week on this patient and we reached the peak of 741 for AST, and 630 for a ALT. Bilirubin, fortunately, remained normal and tolvaptan was never started, and LFTs normalized 4 months later.

In the case to now we had already reached the three times normal AST or ALT, and we stopped tolvaptan. And also, we were really worried about fenofibrate causing this because that was the last added medication. And 5 days later, AST and ALT are up to 130 and 120. So slightly lower than before. And within 4 weeks, LFTs totally normalized. And 2 months later, we actually reinitiated tolvaptan without any problems, and he's been on it for years.

So again, the trigger point of when you stop medication because of suspected liver toxicity is what is called the Hy's law. And Hy's law was defined by Dr. Hyman Zimmerman. And he literally single-handedly defined what would be a practical approach to drug hepatic toxicity. And the take-home message is that if your ALT and AST either are more than three times the upper limit of normal and you have a concomitant increase in the bilirubin more than twice the upper limit of normal without any findings of cholestasis, stones, gallbladder stones, and things like that. In that case, you basically go to the high risk of liver toxicity and maybe, you know, liver failure. And the prognosis would be bad. The mortality in patients who reach that is about 10%. And they need to be really in a liver transplant center for possible pending liver failure.

The graph on the right is the result from actually liver toxicity of tolvaptan. You can see that if you plot the ALT versus peak total bilirubin, the high-risk patients are the ones who are in the right upper corner, the four quadrants that you have, the right upper, and you can only see that in the tolvaptan trial, there was only two of those. And those are really the people that you need to watch very, very carefully. The ones who are below three times normal on ALT, and below two times normal on bilirubin, there are low risk of progressing to liver failure, and that's the low left quadrant. So this is really important to know and you have to really follow the rules and also you have to report if you have liver toxicity, you have to, by law, report it to the FDA through the REMS program so the data will get pulled from the REMS program and will be submitted to the FDA.

To summarize the learning points of these cases. In case one, the chronic kidney pain case, the take-home message is that if you define the indication for interventions at the cyst aspiration, usually it's a very effective mode to decrease the pain but it also has the potential for complications of bleeding and you have to always use the entire range of possibilities that you have to control the pain, not just the procedures.

In case two, the mitigation of polyuria, the new Information, besides the fact that you have to control salt intake is that hydrochlorothiazide could be an effective way to decrease the urine output by almost 25 to 30% in these patients, and that could be the difference between stopping the medication or keep going on it.

And then third series of cases of transaminitis, the take-home message is to follow the Hy's law of who is at high risk of going to liver failure, and monitor them very closely and assess the likelihood of tolvaptan or another cause of liver dysfunction in these patients to make the right decision about stopping or continuing the treatment.

I hope that these cases are helpful for your clinical practice. And thank you very much for your attention.

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