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Addressing the Challenges of Gastroparesis in Patients

Dr. Buch:
Welcome to *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch, and today we're joined by Dr. Michael Camilleri to talk about gastroparesis. He's the lead author of "ACG Clinical Guideline: Gastroparesis," which was published in *The American Journal of Gastroenterology* in August 2022. Dr. Camilleri is a Professor of Medicine, Pharmacology, and Physiology at the Mayo Clinic in Rochester, Minnesota.

Dr. Camilleri, welcome back to the program.

Dr. Camilleri:
Thank you, Peter. It's great to be back with you.

Dr. Buch:
So let's get started, what are the difficulties of diagnosing patients with gastroparesis?

Dr. Camilleri:
Well, that's a great question to start with. The symptoms of gastroparesis are really identical to those of patients who present to us in internal medicine or in gastroenterology with symptoms typically called dyspepsia, symptoms of early fullness after the meal, nausea, sometimes vomiting, upper abdominal bloating, and even upper abdominal pain. So if the symptoms are so similar between dyspepsia and gastroparesis, how should we differentiate the two you might ask.

I think this is where it's really important to have a robust optimal gastric emptying test available. In our practice and in the guidelines, the ACG guidelines of both 2013 and 2022, we specified that based on the consensus and the information available in the literature, the symptoms of dyspepsia and gastroparesis are very similar, as I described earlier, but the presence of delayed gastric emptying of solids and the exclusion of obstruction of the pylorus or the lower end of the stomach is essential to make the diagnosis of gastroparesis, and therefore in practice, we have to have a good gastric emptying test that assesses the emptying of solids. Unfortunately, one of the difficulties that is paramount in clinical practice is that the available gastric emptying tests in different hospitals and clinics around the country really vary considerably.

So what would be an optimal gastric emptying test? It should involve solid food, and it should be conducted for a period of at least three or four hours because that's what tells us about the degree to which the stomach has emptied at that time point, and clinically, that's a relevant time point because that typically is when the patient is going to be taking their next meal and they feel uncomfortable with the next meal.

Ideally, it would be a meal which contains at least 20 percent fat, and also, it is conducted with either samples of breath or with imaging with a gamma camera for at least three hours and ideally four hours.

Dr. Buch:
Can there be false positives or false negatives when undergoing this testing?

Dr. Camilleri:
Absolutely, and that constitutes the difficulty in the diagnosis. So you could have false-positive results, so a commonly performed gastric emptying test involves the use of an egg substitute, called Egg Beaters. This is a usually 250 kilocalorie two percent fat meal. And you could, for example, empty 85 percent of the meal at four hours on one day, and that would be positive for gastroparesis because the normal value is to have emptied 90 percent at four hours. However, there is variation from day to day, and on another day it may be that

the same patient, even a couple of weeks apart, has emptied 92 percent of the meal from the stomach at four hours, in which case we would classify that patient as normal. So in the past, some authorities have recommended that if there is this type of borderline gastric emptying, let's say between five and 15 percent remaining in the stomach at four hours, before embarking upon full treatment of the gastroparesis, one might need to replicate the result to make sure it's consistently either positive or negative.

Dr. Buch:
Thank you. And switching over to therapeutics, what is currently available to treat gastroparesis? And also, what should we know about the risk of developing tardive dyskinesia when we use metoclopramide?

Dr. Camilleri:
Thanks. So metoclopramide is the only medication that's approved by the FDA for the treatment of gastroparesis, but it comes with a black box warning, so we are informed that we should not be prescribing this medication for more than three months. Now of course, the problem with that is that gastroparesis is a chronic condition that may last a long time longer than three months, and so, what is the prescriber supposed to do? Well, unfortunately, the FDA guidance does not tell us what to do after that three-month period of time.

Why is it that there is this restriction on the prescription duration for metoclopramide? And you indicated it in your question. There is a risk of tardive dyskinesia with metoclopramide. Now let's be clear. Tardive dyskinesia is not a reversible involuntary movement. Tardive dyskinesia is an involuntary movement that persists essentially forever. It's irreversible.

Now if you look at the black box warning, it would suggest that the prevalence of tardive dyskinesia is four percent, and I have absolute concerns about that assessment. Why? Well, because several studies have been performed using epidemiological data as well as prescription databases that are available particularly in Northern Europe where such prescriptions have to be recorded in a public database when it's prescribed, or because of national health systems, these data are robustly available for research. And when you look at that type of information, the risk of true tardive dyskinesia, that is irreversible involuntary movement, is probably 1 in 1,000 to 1 in 10,000. It's nowhere near the four percent that is mentioned in the information available to prescribers in the United States. I will acknowledge that four percent is true for reversible involuntary movements, but in that situation you stop the medication, and within a few days the metoclopramide is washed out of the system and the involuntary movement stops. So I think it's important for prescribers to know that the risk of tardive dyskinesia is probably at worst 1 in 1,000. That is tardive dyskinesia that's irreversible.

So I'm going to come back to address the question of—what do I do to prescribe patients with chronic gastroparesis when I'm using metoclopramide? First of all, I use the lowest possible dose that I can get away with. I typically never exceed a dose of 30 or 40 milligrams total per day. That's 10 milligrams before each meal and possibly 10 milligrams before bedtime. Second, in patients with gastroparesis, it may be helpful to prescribe the liquid formula of metoclopramide. Unfortunately, this may not be easily available, and even more unfortunately, it may be more expensive than the tablets. Third, after the three months are over, I ask the patients to contact me. I give them a drug holiday for a couple of weeks. I ask them to go on to a more blenderized or liquidized diet for those couple of weeks, and then I actually re-prescribe the medication for a period of up to three months, but I want to make sure that the patient does not have adverse effects before I re-prescribe the medication. And I always give a two-week holiday from the medication, which also helps me understand how the patient is doing, and also, whether they need the re-prescription of the metoclopramide.

Dr. Buch:
Thank you for that. So, when considering non-FDA-approved medications, what are your thoughts about domperidone? And equally important, how can clinicians obtain it for their patients?

Dr. Camilleri:
So domperidone is not approved in the United States except with a program that requires an application for an investigational drug application, an IND, in order to be able to prescribe it. I think domperidone is a good antiemetic medication. When I and my colleagues review the data of its efficacy as a prokinetic to enhance gastric emptying, it's probably just about as good, but possibly not, as good as metoclopramide, so of the two from a prokinetic and antiemetic perspective, I tend to favor metoclopramide. The other concern about domperidone is that there could be a risk of some cardiac arrhythmias similar to what was the concern regarding cisapride in the past.

So in order to prescribe domperidone, one has to apply for a special dispensation, if you wish, with an IND application, and at my institution it would require us also to register all the patients in a research study and have to report on every patient and all of their adverse effects to our Institutional Review Board, and for that reason it's a major disincentive for many doctors, including myself, to prescribe the domperidone.

Dr. Buch:
Thank you. For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Michael Camilleri about diagnosing and treating patients with gastroparesis.

Now, Dr. Camilleri, what should we know about the use of 5-HT4 agonists?

Dr. Camilleri:
Thanks. 5-HT4 agonists, first of all, how do they work? They work by stimulating the acetylcholine-producing nerves within the wall of the stomach or of the intestine, so it's like you're stimulating the nerve directly to produce acetylcholine to make the stomach muscle contract better.

We do have a 5-HT4 agonist that is approved in the United States, and that is prucalopride, which is approved for the treatment of chronic idiopathic constipation. So if your patient has gastroparesis but also has chronic idiopathic constipation, it would be a good idea to consider treating with prucalopride, acknowledging that this is not a medication that is directly approved for the treatment of gastroparesis. However, studies that we actually did here many years ago at Mayo Clinic had demonstrated that prucalopride accelerates gastric emptying both in healthy volunteers and in patients with chronic constipation, so that would be one approach that could be taken with an approved 5-HT4 agonist even though it's not directly approved for the indication of gastroparesis.

Dr. Buch:
And which patients with gastroparesis are the best candidates for gastric peroral endoscopic myotomy, otherwise known as G-POEM?

Dr. Camilleri:
We still don't have very clear ideas as to evidence-based information regarding the utilization of the gastric POEM procedure. What I see is that this is now becoming a practice for endoscopic pyloromyotomy in patients who are not responding to medical therapy, and as we heard, unfortunately, we do not have much in terms of medical therapies that we can offer. The best advice I can give is that if your gastroenterology practice, or your radiologist perhaps, perform a test called EndoFLIP measurement where the distensibility of the pylorus can be measured with a device like with a balloon on it that assesses the diameter, the circumference, and the distensibility of the pylorus—if that is abnormal, then that might be an indication for treating the pylorus.

Another possibility—but this type of evaluation is only available at very few medical centers—is to actually measure the contractions of the stomach and the pylorus and the duodenum with high-resolution manometry similar to what is done in the esophagus when doctors want to diagnose spasm or achalasia or scleroderma. So if you put a probe with multiple sensors across the antrum, pylorus, and duodenum, you can find out after the patient eats a meal whether the lower part of the stomach, the antrum, is contracting and whether it is producing a frequency of contractions more than one per minute that is able to break down solid food to help it empty from the stomach.

So in summary, perhaps in the future, measuring how the pylorus works and measuring how the lower part of the stomach contracts after a meal will help us choose the right patients for the G-POEM procedure.

Dr. Buch:
And to conclude, Dr. Camilleri, are there any final thoughts you'd like to share with our audience today?

Dr. Camilleri:
I'd like to leave two principles. Number one is try to get an optimal gastric emptying test for solids. Get your nuclear medicine department or perform a breath test which is approved by the FDA, the 13-carbon spirulina breath test. Perform it for a period of four hours so that you can really get a good assessment of gastric emptying.

The second important principle is to remember the importance of focusing on the patient's nutrition. And this is where I say to the patients it's really important that you have a good blender in your kitchen and that you cook any nondigestible fiber, nondigestible vegetables, or fruits. Cook them and then put them in the blender and eat that good food in the liquid form, because ultimately, that's what your stomach is doing to that food, so help your stomach by using the blender and cooking the nondigestible fiber. And also, remember that a very high-fat diet tends to slow the stomach. So the principles are get the right diagnosis and remember to focus on the patient's nutrition.

Dr. Buch:
This was a wonderful update on gastroparesis. And I want to thank my guest, Dr. Michael Camilleri, for sharing his insights.

Dr. Camilleri, it was a pleasure speaking with you again.

Dr. Camilleri:
My pleasure as well. Thank you so much, Dr. Buch.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit ReachMD.com/GIInsights where you can Be

Part of the Knowledge. Thanks for listening, and looking forward to learning with you next time.