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Glucagonlike Peptide-1 Receptor Agonists: The Good, the Bad, and the Ugly—Benefits for Glucose Control and Weight Loss with Side Effects of Delaying Gastric Emptying

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Glucagonlike peptide-1 (GLP-1) receptor agonists (RAs) are being increasingly used for glycemic control in patients with diabetes and for weight loss and weight management in obese subjects. There has been recent public awareness of the potential of GLP-1 RAs to delay gastric emptying and cause gastroparesis. By delaying gastric emptying, these agents can complicate the clinical evaluation of patients on these drugs by affecting diagnostic testing for gastroparesis. This article discusses GLP-1 RAs and their effects on gastric emptying, gastric food retention, and gastroparesis. This article highlights how physicians should be attuned to the gastric side effects of these popular therapeutic agents for blood glucose control in people with diabetes and for weight loss and weight management in obese patients.

Key Words: GLP-1 receptor agonists; gastric emptying scintigraphy; gastroparesis

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Glucagonlike peptide-1 (GLP-1) receptor agonists (RAs) are being increasingly used for glycemic control in patients with diabetes and for weight loss and weight management in obese subjects.

By delaying gastric emptying, these agents can complicate the clinical evaluation of patients by affecting diagnostic testing for gastroparesis. Delaying gastric emptying can also increase the risk of aspiration during endoscopic and surgical procedures (*1,2*). This article discusses GLP-1 RAs and their effects on gastric emptying, gastric food retention, and gastroparesis, as well as highlighting how physicians and other medical staff caring for these patients should be attuned to the gastric side effects of these popular therapeutic agents for blood glucose control in people with diabetes and for weight loss and weight management in obese patients.

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GLP-1 Actions

GLP-1 is a naturally occurring incretin peptide hormone, synthesized primarily in intestinal endocrine cells (*2*). On nutrient ingestion, GLP-1 is released, activating GLP-1 receptors in various target tissues, including the pancreas, stimulating insulin release; the hypothalamus, stimulating satiety centers; and gastric neuronal cells, delaying gastric emptying. GLP-1 RAs are peptides developed to control blood glucose by causing insulin release and slowing gastric emptying, which can result in a sensation of fullness that can reduce appetite. Endogenous GLP-1 has a short half-life of 2–3 min, whereas the pharmacologic GLP-1 RAs that have been developed have extended durations of action for the management of type 2 diabetes mellitus (e.g., semaglutide, dulaglutide, and liraglutide) and weight management (e.g., semaglutide and liraglutide). Table 1 lists the GLP-1 agonists that have been developed. GLP-1 RAs can be classified as short-acting or long-acting depending on how long they work in the body and how frequently they are given. Short-acting and long-acting GLP-1 RAs have different characteristics (*3*). Short-acting GLP-1 RAs stay in the body for less than a day and are generally taken once or twice per day; they help control blood sugar levels after meals. For short-acting GLP-1 RAs, such as exenatide and lixisenatide, delayed gastric emptying is the main mechanism of suppression of postprandial hyperglycemia. Long-acting GLP-1 RAs continue to work for a full day or even a week after being taken and help to control blood sugar throughout the day and night. For the long-acting GLP-1 RAs, such as liraglutide, exenatide long-acting release, dulaglutide, and semaglutide, increasing glucose-dependent insulin secretion and suppressing inappropriate glucagon

TABLE 1
Glucagonlike Peptide-1 RAs Used for Glucose Control and Weight Management

Generic name	Brand name	Dosing	Half-life	Indication
GLP-1 RAs				
Short-acting GLP-1 RA				
Exenatide	Byetta (Eli Lilly)	5–10 μg SQ twice daily	2.4 h	Glycemic control in adults with T2DM
Lixisenatide	Adlyxin (Sanofi)	10–20 μg SQ daily	3 h	Diabetes management in conjunction with insulin
Liraglutide	Victoza (Novo Nordisk)	0.6–1.8 mg SQ daily	13 h	Glycemic control in T2DM
Liraglutide	Saxenda (Novo Nordisk)	0.6–3 mg SQ daily	13 h	Weight loss and chronic weight management
Long-acting GLP-1 RA				
Dulaglutide	Trulicity (Eli Lilly)	0.75–4.5 mg SQ weekly	5 d	Improvement of blood sugar in T2DM
Semaglutide	Rybelsus (Novo Nordisk)	3–14 mg orally daily	7 d	Treatment of T2DM, an oral agent
Semaglutide	Ozempic	0.25 to 2 mg SQ weekly	7 d	Diabetes management; off label for weight management
Semaglutide	Wegovy	0.25–2.4 mg SQ weekly	7 d	Approved by Food and Drug Administration for chronic weight management
Exenatide long-acting release	Bydureon Bcise (AstraZeneca)	2 mg SQ weekly	2 wk	Glycemic control in adults with T2DM
Dual glucose-dependent insulinotropic polypeptide/ GLP-1 RAs				
Tirzepatide	Mounjaro	2.5–15 mg SQ weekly	5 d	Treatment for T2DM; off label for weight loss
Tirzepatide	Zepbound (Eli Lilly)	5–15 mg SQ weekly	5 d	Treatment for obesity

SQ = subcutaneously; T2DM = type 2 diabetes mellitus.

secretion are the main mechanisms of suppression of postprandial hyperglycemia.

In recent years, the number of patients with diabetes treated with GLP-1 RAs has increased. Many endocrinologists are using these GLP-1 RAs and sodium–glucose cotransporter 2 inhibitors. Several societies have recommended earlier initiation of these medications, especially in patients with cardiovascular or renal disease (*4,5*). Although gastrointestinal symptoms such as nausea and vomiting and delayed gastric emptying are labeled side effects of the GLP-1 RAs, there are limited reports of actual medication-induced gastroparesis reported.

Drug development has led to strategies to further improve the efficacy of GLP-1 RAs. Dual glucose-dependent insulinotropic polypeptide/GLP-1 RAs have been recently developed, of which tirzepatide is an example (*6*). Because of the complementary actions of the 2 incretins, these compounds may offer improved management options for type 2 diabetes mellitus and obesity. Nausea and delayed gastric emptying are reported side effects of tirzepatide. The gastric emptying delay is largest after the first dose, and this effect diminishes over time. Tirzepatide slows postmeal glucose absorption, reducing postprandial glucose.

GLP-1 and Gastric Emptying and Gastroparesis

Liraglutide is a long-acting GLP-1 RA that activates glucagon receptors on pancreatic β-cells to stimulate glucose-dependent insulin action. Subcutaneous injection of up to 1.8 mg once daily is used for glucose control, whereas higher doses are used for chronic weight management (Table 1). Liraglutide use is associated with slower gastric emptying and increased fasting gastric volume (*7*). In a prospective randomized, placebo-controlled trial of liraglutide in adult patients with obesity and normal gastric emptying at baseline, liraglutide, 3 mg subcutaneously daily, increased weight loss at 5 and 16 wk of treatment and slowed gastric emptying at these times compared with placebo (*7*). Overall, 57% of patients treated with liraglutide developed delayed gastric emptying. In patients developing delayed gastric emptying at 5 wk, 51% of the patients had a persistent delay in gastric emptying to 16 wk. Conversely, of the patients with delayed gastric emptying at 5 wk, 49% of the patients normalized their gastric emptying at 16 wk. Tachyphylaxis due to persistent use of the GLP-1 RA has been suggested as a potential explanation for the initial delay in gastric emptying, with subsequent improvement with continued treatment in some patients.

Case reports have described patients being diagnosed with gastroparesis who had recently started GLP-1 RAs. Rai et al describe a case of liraglutide-induced acute gastroparesis in a 52-year-old man with type 2 diabetes mellitus presenting with symptoms of gastric outlet obstruction (*8*). Treatment involved initial nasogastric suction and discontinuation of liraglutide. Kalas et al. published 2 cases of medication-induced gastroparesis that were initially diagnosed as diabetic gastroparesis but were subsequently found to have been induced by GLP-1 RAs (*9*). Repeat studies after medication discontinuation found improvement in symptoms and resolution of the delayed gastric emptying. In each of these cases, the association of the GLP-1 RAs with the gastroparesis was recognized not initially but only on careful review of medications the patient was taking after presentation. These case reports emphasize the potential to mislabel patients with gastroparesis who have a gastric emptying test performed while taking a GLP-1 RA.

Further research needs to be done to assess the frequency of misdiagnosing diabetic patients with gastroparesis due to medications, specifically GLP-1 RAs. In a review of gastric emptying scintigraphy (GES) tests performed over 2 y (2019–2021), Kalas et al. found that of 384 tests performed, 57% of the patients had diabetes and 24% of the patients with diabetes were on a GLP-1 RA (*10*). Of the patients with diabetes with delayed gastric emptying, 24% were on a GLP-1 RA. This study did not find an association between GLP-1 RA use and delayed gastric emptying. Some studies have reported that the effect of GLP-1 RAs on gastric emptying is more pronounced in the first hour of gastric emptying than at later times postprandially (3 and 4 h).

The association of GLP-1 RAs and delayed gastric emptying is not new. The American College of Gastroenterology guidelines for gastroparesis, published in 2013 (*11*), describe iatrogenic gastroparesis from pharmacologic agents such as narcotic opiate analgesics, anticholinergic agents, and some diabetic medications, including GLP-1 RAs. The most common side effects of GLP-1 RAs are nausea and vomiting, which have been attributed to delayed gastric emptying. Nausea (43.5%) was the most commonly reported adverse event with exenatide treatment, and vomiting was also quite commonly encountered (12.8%) (*12*). These guidelines suggest that for accurate determination of gastric emptying, GLP-1 RAs should be withdrawn before patients undergo a gastric emptying test to evaluate for gastroparesis. Usually, medications that have the potential to delay or even speed up gastric emptying are held for 3–4 half-lives of the drug. For narcotic analgesics, this is often 2–3 d. Three days off treatment would be for the short-acting GLP-1 RAs, which are given on a once- or twice-daily basis, but it would be 3–4 wk for the long-acting GLP-1 RAs, which are often given on a weekly basis, as is more typically done for weight reduction in an obese patient. There is some evidence to suggest that GLP-1 RAs may impair gastric emptying for up to 8 wk (*13*).

Limited studies are available evaluating the use of GLP-1 RAs in patients with preexisting gastroparesis. Beti et al., from Germany (*14*), conducted one of the few studies evaluating the effect of GLP-1 RAs on patients with diabetes with and without preexisting diabetic gastroparesis. In the study, 75% of participants with normal gastric emptying before receiving GLP-1 RAs developed delayed gastric emptying. In addition, 30% of participants with preexisting diabetic gastroparesis had worsening gastric emptying after GLP-1 RA treatment, whereas the remaining 70% had no change or minimal improvement. Linnebjerg et al. reported a dose-dependent delay in gastric emptying in patients with type 2 diabetes mellitus treated with exenatide (*15*). The diabetic patients with slower baseline gastric emptying had less change in gastric emptying after exenatide administration.

The Food and Drug Administration has recently received reports of stomach paralysis, or severe gastroparesis, developing with the antiobesity GLP-1 RA drugs semaglutide and liraglutide (*16*). Surprisingly, some patients have reported that the gastroparesis did not resolve after cessation of the drug, an event that usually does not occur with RAs. Recently, the Food and Drug Administration has added the potential side effect for Ozempic (Novo Nordisk) of ileus or blockage of intestinal contents. This is already present in the label for Wegovy (Novo Nordisk) and Mounjaro (Eli Lilly).

In patients with diabetic gastroparesis, optimal glucose control is suggested to reduce the future risk of complications of diabetes, including gastroparesis. In some patients, glucose control is achieved by use of the GLP-1 RAs. Thus, the GLP-1 RAs are helpful on one hand for glucose control and weight management but may be potentially harmful on the other hand, causing delayed gastric emptying, gastric retention, and gastroparesis symptoms.

GLP-1 Agonists and Gastric Emptying Testing

GES is considered the gold standard for quantifying gastric emptying and diagnosing gastroparesis. Gastric emptying should be assessed when patients have relatively good glucose control because hyperglycemia can itself delay gastric emptying. The current procedure guideline (*17*) and consensus recommendations (*18*) of the Society of Nuclear Medicine and Molecular Imaging and the American Neurogastroenterology and Motility Society for performing GES indicate that imaging centers should check the fasting glucose level on the day of gastric emptying testing to make sure the blood glucose is under control. Although the recommended upper level for serum glucose before performing the test varies slightly between the 2 publications ($<$200 mg/dL (*17*) and $<$275 mg/dL (*18*)), an upper limit of less than 275 mg/dL is generally considered acceptable. Both publications recommend that drugs that can potentially delay gastric emptying should be withheld before a gastric emptying test is performed. However, they give no specifics on how to approach symptomatic patients currently on newly developed GLP-1 RA drugs. With a long half-life of up to 7 d for drugs in common use, this has led to controversy and confusion on how and when to study symptomatic patients who would need to be off their medication for at least 2–3 half-lives.

Most physicians and patients are not willing to withhold these medications for such a long time (3–4 wk).

GLP-1 RAs and Aspiration

In delaying gastric emptying, and with resulting prolonged retention of food in the stomach, these agents might increase the risk of aspiration in patients sedated for endoscopic and surgical procedures. In a retrospective analysis of patients undergoing elective upper endoscopy (*19*), increased residual gastric contents were seen in 8 of 33 (24%) patients receiving semaglutide, compared with only 19 of 371 (5%) patients not receiving semaglutide ($P < 0.001$). Semaglutide use and the presence of preoperative digestive symptoms (nausea/vomiting, dyspepsia, abdominal distension) were associated with increased residual gastric contents. One case of pulmonary aspiration was reported, with that patient being in the semaglutide group. Additional studies have confirmed that GLP-1 RA treatment has been associated with gastric residue in an esophagogastroduodenoscopy in patients with diabetes, with the proportion of gastric residue higher in the GLP-1 RA treatment group than in the non–GLP-1 RA treatment group (5.4% vs. 0.5%) (*3*).

The potential risk of aspiration associated with delayed gastric emptying is of particular concern to anesthesiologists sedating these patients for endoscopy and surgical procedures. Several published case reports have documented instances of aspiration in patients receiving GLP-1 RAs, emphasizing the importance of considering this risk (*1,2*). Several suggestions in the anesthesiology literature have been made for patients taking these medications. One is guidelines on stopping these agents before surgical procedures: to hold the short-acting agents for a day and the long-acting agents for a week (*1*). Another is to consider performing gastric ultrasound to determine residual gastric content before induction of anesthesia in these patients (*1*). Concern was raised since the GLP-1 RAs are often given weekly and often stored in a refrigerator at home; the patient might not report this to the surgeon at the time of the evaluation but may report this to the anesthesiologist on the day of surgery.

Suggestions for Managing Patients Taking GLP-1 RAs

Questions remain on how to deal clinically with patients taking GLP-1 RAs, with their potential to delay gastric emptying, since these agents have ramifications in diagnosing gastroparesis and in performing procedures on patients taking these medications. Here are some suggestions that seem appropriate from the information presented above.

Patients Being Considered for Treatment with a GLP-1 RA. We suggest that patients should be assessed for symptoms of gastroparesis (nausea, vomiting, stomach fullness) before starting treatment with a GLP-1 RA. If symptoms of gastroparesis are present, consider obtaining a gastric emptying test to document delayed gastric emptying before treatment with a GLP-1 RA. Once patients are taking the GLP-1 RA medications (similar to patients starting to take narcotic analgesics), it will be difficult to discern whether they have true gastroparesis or medication-induced gastroparesis. Interestingly, the patients who use them for glucose control in type 2 diabetes mellitus are often at risk for developing gastric emptying abnormalities, primarily gastroparesis, but occasionally rapid gastric emptying can be seen (*20*). Of note, these agents are now being used much earlier in the course of the diabetes and may actually prevent gastroparesis by improving glucose control. If symptoms or delayed gastric emptying is present before treatment, proceed with caution with use of a GLP-1 RA, as symptoms and gastric emptying may worsen on treatment.

Patients being treated with a GLP-1 agonist should be told about potential side effects, that they may develop symptoms such as nausea and fullness, and that these medications can delay gastric emptying. Furthermore, patients should be reminded to tell their physicians that they are on these medications, especially gastroenterologists performing endoscopic procedures, surgeons for surgical procedures, and anesthesiologists sedating the patients for these procedures. These patients should also be instructed to inform other health care providers such as nuclear medicine technologists about such medications, especially before studies such as GES.

Patients Developing Gastrointestinal Symptoms on a GLP-1 RA. If a patient being treated with a GLP-1 RA develops persistent symptoms of gastroparesis—nausea, vomiting, fullness—then the medication should probably be stopped to see whether the symptoms resolve. If they do, providers may need to prescribe a different method of drug control of glucose. If the symptoms do not resolve after the GLP-1 RA is stopped, then evaluation for gastroparesis off the GLP-1 RA is suggested.

Patients on GLP-1 RAs Being Considered for GES. Physicians ordering gastric emptying tests should be aware of whether the patient is taking a GLP-1 RA, just as they should know whether patients are taking narcotic analgesics or are heavy users of cannabis (marijuana), which also delays gastric emptying. The best practice for physicians ordering the test is to have the patient stop these medications before any test to measure gastric emptying. This stoppage should last 3–4 d for patients taking a short-acting, once- or twice-daily GLP-1 RA but 3–4 wk for patients taking a long-acting, often weekly GLP-1 RA. Stopping the GLP-1 RA may be difficult, as it takes time to come off the pharmacologic effects of the GLP-1 RA, and the patient might lose glucose control. Any such decision must be carefully considered between both the patient and the physician.

When patients present to the nuclear medicine department for a gastric emptying test, the current medications of the patients should be reviewed, including ones that can accelerate or delay gastric emptying, such as narcotic pain medications, anticholinergic agents, and GLP-1 RAs. The patient should inform the testing site of use of these medications before testing, and a decision should be made with the referring physician on whether to proceed that day or reschedule the test and, if the latter, for how long the drug should be withheld.

If a GES test is performed on a patient taking a GLP-1 RA, the GES report should state this and indicate that any delay in gastric emptying may be drug-induced. For patients referred for GES with symptoms of gastroparesis and who are taking a GLP-1 RA, the test will not be able to differentiate between delayed gastric emptying caused by diabetic gastroparesis and delayed gastric emptying caused by medication-induced gastroparesis. If GES is performed on patient receiving a GLP-1 RA, a normal result rules out both, allowing one to potentially look for other causes. However, symptoms may still be from the GLP-1 RA despite no delay in gastric emptying, perhaps through effects of GLP-1 RA on the vagus nerve. If gastric emptying is delayed, one therapeutic option would be to stop the medication and see whether the symptoms resolve. If the symptoms do not resolve, patients might need to undergo an additional gastric emptying test after a sufficient time (as much as 4 wk) off the medication to see whether they still have true gastroparesis.

Patients on GLP-1 RAs Who Are Undergoing Endoscopic or Surgical Procedures. Because the GLP-1 RAs delay gastric emptying and increase gastric retention, retained food in the stomach could be aspirated in patients being sedated for procedures. For patients taking GLP-1 RAs, consider holding the drug for at least 3 half-lives before a planned procedure (*21*). For semaglutide, this would be 3 wk. Generally, for these procedures, the patient reports fasting overnight. Often, if patients are known to have gastroparesis, they are instructed to be on a liquid diet for 1–3 d before their procedure to reduce the chance of gastric solid-food retention. This preparation could also be used for patients on GLP-1 RAs. For patients taking GLP-1 RAs for type 2 diabetes mellitus, consider consulting the provider prescribing the agent about the risks and benefits of holding the drug for at least 3 half-lives ahead of the planned procedure.

SUMMARY

GLP-1 RAs are being increasingly used for glycemic control in patients with diabetes and for weight loss and weight management in obese subjects.

By delaying gastric emptying, these agents can complicate the clinical evaluation of patients on these drugs by affecting the diagnostic testing for gastroparesis. Delaying gastric emptying can also increase the risk of aspiration during endoscopic and surgical procedures. Physicians, health care providers, and medical staff caring for these patients should be attuned to the gastric side effects of these popular therapeutic agents.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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