Implications of GLP-1 Agonists on Office-Based Sedation and General Anesthesia for Dentistry

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Incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are produced in the gut and play critical roles linking the processes of eating and digestion with the release of insulin from the pancreas and glucose homeostasis. GLP-1 receptor agonist and combination GLP-1/GIP receptor agonist medications are exogenous incretins that mimic their endogenous counterparts, but their significantly longer half-lives allow them to be clinically useful for managing diabetes mellitus type 2 (DMT2) and obesity. Recently, their use for weight loss has grown exponentially, increasing the potential that a provider of sedation or general anesthesia for dentistry will encounter a patient taking a GLP-1 or GLP-1/GIP combination receptor agonist. One of the clinical effects produced by these medications is decreased gastric emptying which increases satiety and decreases oral intake. While these medications are effective in the management of DMT2 and obesity, delayed gastric emptying can cause concerns for sedation and general anesthesia providers. Retained gastric contents can increase risks for emesis and subsequent pulmonary aspiration in the perioperative period. In 2024, a multisociety guidance document was published to provide recommendations for the management of these patients in the perioperative period. Recommendations emphasized risk stratification of individual patients and weighing the risks vs the benefits of holding or continuing GLP-1 and GLP-1/GIP combination receptor agonist medications. The recommendations also suggested shared decision making between the sedation or general anesthesia provider, the prescribing physician, and the patient should be used when developing a plan regarding the preoperative use of these medications.

Key Words: GLP-1 receptor agonist; GIP receptor agonist; Semaglutide; Tirzepatide; Diabetes mellitus type 2; Obesity.

Glucagon-like peptide-1 (GLP-1) and combination GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist medications (Table) mimic natural incretin hormones produced by the gut that have a critical role in digestion and glucose homeostasis. These classes of medications have promising roles in the treatment of diabetes mellitus type 2 (DMT2) and obesity. In fact, GLP-1 receptor agonists were the fastest growing class of diabetic medications in 2022. While new prescriptions of these medications for DMT2 increased 128%, it may be of more interest that new prescriptions for obesity grew 352% during this time.[1] With the rapid increases in prescriptions for DMT2 and weight loss management, a growing number of patients on these medications are presenting to dental offices for treatment under sedation or general anesthesia. It is important for all providers of sedation or general anesthesia for dentistry to understand the mechanisms of action and potential clinical ramifications of these novel medications. One of the clinical effects of GLP-1 receptor agonists is delayed gastric emptying which helps increase satiety and curb eating. However, delayed gastric emptying can be a major concern for sedation and general anesthesia providers as patients on these medications can present with substantial residual gastric content despite their compliance with routine preoperative fasting guidelines. This can put such patients at higher risk for emesis and pulmonary aspiration while sedated or generally anesthetized. The resulting effects of these medications on a patient's physiology may influence clinical management decisions when optimizing a patient for sedation or general anesthesia.

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REVIEW OF INCRETINS AND GLUCOSE HOMEOSTASIS

Incretins are endogenous hormones produced by the gut that play critical roles linking the processes of eating and digestion

Table. Summary of GLP-1 and GLP-1/GIP Receptor Agonists.[2,6,9]

Medication	*Class*	*Indication*	*Decrease in HBA1C*	*Half-life*	*Dosing schedule*
Dulaglutide (Trulicity)	GLP-1 RA	DMT2	1–1.5	4.5–4.7 d	SQ injection/wk
Exenatide IR (Byetta)	GLP-1 RA	DMT2, obesity	1.0	2.4 h	SQ injection twice/d
Liraglutide, 3 mg (Saxenda)	GLP-1 RA	Obesity	N/A	13 h	SQ injection/d
Liraglutide, 1.2 mg/1.8 mg (Victoza)	GLP-1 RA	DMT2	0.8–1.5	13 h	SQ injection/d
Lixisenatide (Adlyxin)	GLP-1 RA	DMT2	0.8–1.0	3 h	SQ injection/d
Semaglutide (Ozempic)	GLP-1 RA	DMT2	1.5–2.0	1 w	SQ injection/wk
Semaglutide (Wegovy)	GLP-1 RA	Obesity	N/A	1 w	SQ injection/wk
Semaglutide (Rybelsus)	GLP-1 RA	DMT2	0.7–2	1 w	Oral pill/d
Tirzepatide (Mounjaro)	GLP-1/ GIP RA	DMT2	2–2.5	5 d	SQ injection/wk

Abbreviations: DMT2, diabetes mellitus type 2; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; IR, immediate release; RA, receptor agonist; SQ, subcutaneous.

with the release of insulin from the pancreas and glucose homeostasis. Two of the main incretins are GLP-1 and GIP which work along with insulin, glucagon, and somatostatin in helping to closely regulate blood glucose levels. With each meal, the ingestion of carbohydrates, proteins, and fats triggers the release of GLP-1 and GIP. Patients with DMT2 have an imbalance in the regulation of these incretin hormones.[2]

Glucagon-like Peptide-1 (GLP-1)

GLP-1 is primarily produced in the enteroendocrine L cells in the small intestine and colon, although pancreatic alpha cells produce small quantities as well. Once released, GLP-1 acts to increase insulin secretion from beta cells in the pancreas which helps lower blood glucose levels. However, GLP-1 also has other important actions such as promoting somatostatin release from pancreatic delta cells, which in turn counteracts or inhibits the secretion of glucagon from alpha cells of the pancreas. GLP-1 also works to slow gastric motility, delaying emptying of the stomach and the absorption of carbohydrates from the gut. It also plays a role in helping to regulate fat deposition in adipose tissue.[3] Endogenous GLP-1 has a short half-life of approximately 2 minutes due to rapid degradation by dipeptidyl peptidase-4 (DPP-4) and neutral endopeptidase.[4]

Glucose-dependent Insulinotropic Polypeptide (GIP)

GIP is produced primarily by enteroendocrine K-cells in the small intestine, specifically those within the duodenum and jejunum, and acts on specific receptors located in many of the same areas in which GLP-1 acts. These receptors are found in the pancreas, bone, adipose tissue, and heart. Like GLP-1, GIP stimulates insulin production from pancreatic beta cells, effectively reducing blood glucose, and helps regulate fat deposition. However, GIP on its own increases glucagon activity and has no effect on gastric emptying.[3]

Dipeptidyl Peptidase-4 (DPP-4)

DPP-4 is an endogenous enzyme that is found in hepatocytes, intestinal membranes, kidneys, capillary endothelium, and blood plasma. As an exopeptidase, DPP-4 cleaves the peptide bonds of GLP-1 and other incretin hormones, releasing a single amino acid or dipeptide from the peptide chain.[4] DPP-4 is regulated at many levels including gene expression, interaction with proteins, and modulation of enzymatic activity. Changes in DPP-4 activity is associated with obesity and DMT2 as well as other neurologic and inflammatory diseases. Patients with DMT2 and obesity often have increased levels of DPP-4, increasing the cleavage and deactivation of incretin proteins (ie, GLP-1). This leads to an imbalance of incretin activity in these patients, resulting in impaired glycemic control due to a decrease of insulin and an increase in blood glucose. As part of the treatment of DMT2, patients may be taking a DPP-4 inhibitor, such as sitagliptin, with the goal to increase function of their endogenous incretin hormones.[2]

GLP-1 AND GLP-1/GIP RECEPTOR AGONIST MEDICATIONS

Endogenous incretin hormones play a vital role in maintaining homeostasis with the regulation of insulin and glucose. GLP-1 and GLP-1/GIP receptor agonist medications are exogenous incretins that mimic the same effects of their endogenous counterparts. While these medications have the same physiologic effects as endogenous incretins, they have been engineered to have a significantly longer half-life (Table) compared with endogenous incretins, making these medications clinically useful in the management of DMT2 and obesity.

GLP-1 receptor agonist medications activate GLP-1 receptors on pancreatic beta cells, resulting in the release of insulin. The release of glucagon from the pancreas is also inhibited by GLP-1 receptor agonists. These medications also act on receptors in the hypothalamus, resulting in suppression of appetite. GLP-1 receptor agonist medications slow gastric emptying, which further contributes to a feeling of satiety and reduces

oral intake. All these changes lead to a decrease in plasma glucose levels which benefits the patient with DMT2. Numerous other health benefits of these medications include the cardiovascular benefits from decreased blood pressure, decreased low-density lipoprotein levels, and improved endothelial function and perfusion.[2,5]

The extent to which GIP receptor activation on its own is a viable treatment for DMT2 and obesity remains uncertain. GIP receptor agonists are thought to have limited potential as sole therapy for DMT2, although further investigation is ongoing. GLP-1 and GIP receptor agonists in combination have been found to have additive therapeutic effects. The addition of a GIP receptor agonist allows for a lower dose of a GLP-1 receptor agonist to be used when combined, resulting in fewer side effects when compared with medications targeting GLP-1 receptors alone.[2] Tirzepatide (Mounjaro, Eli Lilly) is a dual GLP-1 and GIP receptor agonist medication that depends heavily on GIP agonism. It has a long half-life, thus allowing it to be administered by injection once a week. Patients are often prescribed tirzepatide if they cannot tolerate a GLP-1 receptor agonist medication due to gastrointestinal (GI) symptoms.[2,6]

PERIOPERATIVE COMPLICATIONS FROM GLP-1 AND GLP-1/GIP RECEPTOR AGONIST USE

The novelty of these medications has resulted in a rapid, exponential increase in new GLP-1 and GLP-1/GIP receptor agonist prescriptions in the United States.[7] The known mechanism of action and clinical effects of GLP-1 receptor agonists have suspected implications on standard preoperative fasting guidelines for elective procedures involving sedation or general anesthesia. Specifically, GLP-1 receptor agonist medications are designed to delay gastric emptying to increase satiety. With delayed gastric emptying, providers of sedation and general anesthesia should be concerned about patients having residual gastric content despite adherence to traditional preoperative fasting guidelines. This leads to concerns of perioperative emesis which could result in pulmonary aspiration of a critical volume of acidic stomach contents.

Early evidence is limited to case reports, resulting in the lack of definitive management guidelines for patients on GLP-1 or GLP-1/GIP receptor agonists.[5] The Anesthesia Patient Safety Foundation has described two case reports in detail. In one case, a patient taking semaglutide (Ozempic; Novo Nordisk) had a point-of-care gastric ultrasound prior to sedation for an imaging study. The ultrasound revealed the presence of solid gastric contents despite the patient fasting from solid foods for over 18 hours. The anesthesiologist made the decision to cancel the sedation due to concern for pulmonary aspiration. Another case describes a patient on tirzepatide (Mounjaro; Eli Lily) who fasted the night before surgery. This patient had significant emesis of complex gastric contents prior to extubation that was consistent with what she had eaten days before the procedure. However, the patient's airway was protected when the emesis occurred, so any pulmonary aspiration concerns were mitigated. She recovered in the postanesthesia care unit uneventfully following extubation. An additional case report describes a pulmonary aspiration event after the patient fasted preoperatively for 18 hours. Retrospective reviews of patients undergoing endoscopy have suggested retained solid gastric contents despite otherwise appropriate fasting times.[5]

Although the existing level of evidence with these new medications is limited in quality, the known mechanisms of action and current case reports indicate that patients taking GLP-1 or GLP-1/GIP receptor agonists are at a higher risk for retaining complex solid gastric contents despite following American Society of Anesthesiologists (ASA) preoperative fasting guidelines. This seemingly places such patients at higher risk for pulmonary aspiration and related perioperative complications.[5]

While pulmonary aspiration is a rare occurrence, it is a potentially avoidable adverse event that can have devastating consequences. From a liability perspective, pulmonary aspiration is one of the top 3 airway adverse events as described in an ASA closed claims project.[5] Knowledge of the mechanisms of action and clinical effects of these incretin-based medications is essential, and anesthesia providers must be aware that patients on these medications have an increased pulmonary aspiration risk.

ANESTHETIC CONSIDERATIONS

Adjustments should be made in the anesthetic plan to optimize these patients. For patients at a higher risk of pulmonary aspiration, the ASA suggests considering GI stimulants such as metoclopramide which has been shown to reduce gastric volume and pH perioperatively.[8] Additionally, histamine-2 receptor antagonists (eg, famotidine) and proton pump inhibitors (eg, omeprazole) may be considered to potentially reduce gastric volume and acidity. Finally, preoperative nonparticulate antacids should also be considered, as they decrease gastric acidity.[8]

Considerations to reduce the risk of emesis for patients taking GLP-1 or GLP-1/GIP receptor agonist medications would include avoiding or limiting emetogenic agents. These include volatile anesthetics, nitrous oxide, ketamine, and opioids. Opioids should particularly be avoided in these patients due to their contribution to delayed gastric motility. Regarding antiemetics, the routine prophylactic use of ondansetron (a 5-HT3 receptor antagonist) and dexamethasone along with an additional antiemetic of another type, such as diphenhydramine (an H1 receptor antagonist) or aprepitant (an NK-1 receptor antagonist), could be considered to further reduce the risk of emesis. Depending on patient-specific factors and associated risks, anesthesia providers could consider treating these

patients as if they have a full stomach. Therefore, if intubation is considered, it could be accomplished with a rapid sequence induction, stomach decompression with an orogastric (OG) tube, and an awake extubation.[5]

GLP-1 receptor agonists have known associated risks for the adverse effects of nausea, vomiting, dyspepsia, abdominal distention, and delayed gastric emptying.[9] The use of GLP-1 receptor agonists is less common in pediatrics and has primarily been used for the management of DMT2 and obesity in patients 10 to 18 years of age. In literature published thus far, children on GLP-1 receptor agonists have similar GI adverse events at rates comparable to adults while under deep sedation or general anesthesia.[9] In August 2023, the ASA published the first set of guidelines for consideration in patients taking GLP-1 receptor agonists prior to a scheduled elective procedures[9]:

- For patients on daily, typically oral, dosed GLP-1 receptor agonists, consider holding their dose on the day of the procedure.
- For patients on weekly dosed GLP-1 receptor agonists, consider holding their dose a week prior to the procedure.
- If the GLP-1 receptor agonist is being utilized for DMT2 management and holding a dose would impact their dosing schedule, consult the patient's primary care physician or endocrinologist for bridging antidiabetic therapy to avoid hyperglycemia.

Current Recommendations

In October 2024, the ASA issued an Affirmation of Value for a more recent multisociety guidance document on GLP-1 receptor agonists. This new guidance recognizes the inconsistencies in clinical care guidelines between associations leading to uncertainty on how to safely treat patients taking these medications. The objective of the multisociety guidance is to offer unified guidance for clinicians for managing patients taking GLP-1 medications, regardless of indication, which currently includes DMT2, weight management, and heart failure.[10]

- Recommendation 1: Shared decision making between procedural, anesthesia, and prescribing team should be used to determine the perioperative use of GLP-1 medications. Patient-specific factors should be considered when assessing the risks of these patients for delayed gastric emptying and pulmonary aspiration. Patients in the escalation phase, taking higher doses of these medications, or on weekly dosing are at higher risk for delayed gastric emptying and GI side effects. This is compared with patients in the maintenance phase, taking a lower dose, or on daily oral dosing who are at lower risk for delayed gastric emptying. Additionally, GI symptoms on the day of the procedure are suggestive of delayed gastric emptying. These symptoms include nausea and vomiting, abdominal pain or distension, constipation, or feeling full.[10] The GI side effects of GLP-1 receptor agonists are common, but these symptoms commonly decrease with continued use due to tachyphylaxis.[9] Finally, other medical conditions that impact gastric emptying, such as gastroparesis, bowel dysmotility, chronic opioid use, obesity, and Parkinson's disease, should also be considered as a confounding factor.[10]

In patients with lower risk, GLP-1 medications can be continued in the perioperative period without increased risk for delayed emptying and pulmonary aspiration. In higher risk patients, holding GLP-1 medications should balance risk vs benefit of surgical and medical risks and metabolic disease states. If the decision to hold GLP-1 medications is made, it is suggested to follow the original guidance of the ASA: hold daily formulations the day of surgery and weekly formulations a week prior to surgery.[9,10]

- Recommendation 2: Efforts should be made to minimize the pulmonary aspiration risk of delayed gastric emptying in the perioperative period. For higher risk patients, this could include perioperative diet modification of a liquid diet for 24 hours. When there is a concern for retained gastric contents on the day of the procedure, point-of-care gastric ultrasound can be used to assess volume of gastric contents and pulmonary aspiration risk. Finally, if there is a concern of retained gastric contents, shared decision making with the patient and care team should be used to determine risk vs benefit of delaying the procedure vs rapid sequence induction and tracheal intubation.[10]

In addition to case reports and guidance from various professional associations, there have been multiple retrospective reviews of patients taking GLP-1 receptor agonists undergoing endoscopy that suggest an increased risk of retained gastric contents in patients taking these medications.[5] Medications within this class have relatively long half-lives and stopping these medications for at least 5 half-lives before surgery to allow normalization of gastric function is often not practical. The potential cardiovascular benefits and negligible risk for hypoglycemia that these medications pose have contributed to the thought process of continuing this class of medications without perioperative interruption.[5]

With the limited published data, it is important to review current relevant literature and re-evaluate traditional fasting guidelines in patients taking GLP-1 and GLP-1/GIL receptor agonist medications. The recent popularity of these drugs will hopefully result in more data that may aid providers of sedation and general anesthesia in developing a more systematic approach to assessing risk in this patient population.

Considerations for Office-Based Anesthesia for Dentistry

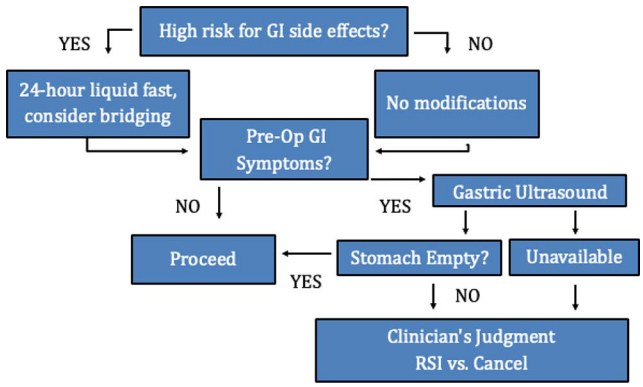
The clinical management of patients taking GLP-1 receptor agonists involves weighing the risks of delayed gastric emptying and pulmonary aspiration with the benefits of perioperative glucose control and improved cardiovascular health. In the preoperative period, the 2024 multisociety guidance document provides the most up-to-date recommendations for anesthesia providers.

If the patient is at high risk for GI side effects and delayed gastric emptying, a 24-hour fast should be considered as well as the use of shared decision making to decide if the GLP-1 medication should be held. If the patient is low risk, no preoperative modifications are likely needed.[10] On the day of the procedure, the anesthesia provider should complete a thorough interview to assess the patient for GI symptoms, including nausea, vomiting, retching, diarrhea, abdominal bloating, or abdominal pain. The presence of these symptoms is concerning for delayed gastric emptying. If the patient has no GI symptoms and is low risk, it is recommended to proceed with the procedure. However, if the patient is symptomatic and there is concern for retained gastric contents, a point-of-care gastric ultrasound can be used to assess pulmonary aspiration risk. If ultrasound is available and no gastric contents are appreciated, it is recommended to proceed with the procedure.[10]

While gastric ultrasound may be helpful, it is unlikely to be practical (ie, not available) in the outpatient dental setting. If an ultrasound of the stomach cannot be obtained and there are concerns about retained gastric contents and increased pulmonary aspiration risk, the ASA recommends to either delay the procedure or to proceed as if the patient has a "full stomach" and to manage accordingly.[9] ASA does recognize that no evidence supports an optimal duration of fasting for patients on GLP-1 receptor agonists.[5,9] Refer to the Figure for a summary of clinical decision making for patients on GLP-1 medications.

To reduce the risk of pulmonary aspiration preoperatively, the anesthesia provider could consider the use of gastric stimulants, histamine-2 receptor antagonists, proton pump inhibitors, and nonparticulate antacids. Antiemetics such as ondansetron, dexamethasone, aprepitant, and diphenhydramine should be considered. Emetogenic medications, such as nitrous oxide, volatile anesthetics, and ketamine should be minimized. Consideration for opioid-sparing strategies should also be made due to the known emetogenic effects of opioids and their further reduction of gastric motility. Intubation with a rapid sequence induction including stomach decompression with an OG tube is the preferred airway management strategy for patients with a full stomach. However, this may not be practical in all dental office settings. If rapid sequence induction is impractical given the practice environment, these patients should be seen under local anesthesia or possibly under light levels of sedation to help ensure their airway reflexes remain intact.

Figure. Summary of Clinical Decision Making for Patients on GLP-1 Medications



This flowchart is based on the 2024 multisociety guidance document for managing patients on GLP-1 medications10 and should be adapted as needed for patient care in the office-based environment.

CONCLUSION

GLP-1 and GIP/GLP-1 receptor agonists mimic endogenous incretins and are used in the treatment of DMT2 and obesity. Dentists providing sedation and general anesthesia for these patients must remain vigilant as they may have retained gastric contents due to delayed gastric emptying. These medications may place patients at higher risk for perioperative emesis and pulmonary aspiration. A recent 2024 multisociety guidance document provides recommendations for patient optimization prior to a procedure utilizing sedation or general anesthesia. This new guidance emphasizes risk stratification based on patient-dependent factors and weighing the risks vs the benefits of holding or continuing these medications. Shared decision making should be used between the anesthesia provider, prescribing physician, and patient when developing a plan.

While these strategies help optimize patients for anesthesia-related care, they do not eliminate all risks for GLP-1 medication-related perioperative complications. The anesthesia provider should consider the risks vs benefits of holding these medications, the presence of GI symptoms on the day of the procedure, and the availability of resources in the individual practice environment. Providers of sedation and anesthesia for dentistry are likely to continue to encounter and treat more patients taking these medications. It is important to fully understand how GLP-1 and GLP-1/GIP receptor agonists impact anesthetic management to provide high quality office-based anesthesia care.

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CE QUESTIONS FOR THE GLP-1 AGONISTS REVIEW

This continuing education (CE) program is designed for dentists who desire to advance their understanding of pain and anxiety control in clinical practice. After reading the designated article, the participant should be able to evaluate and use the information appropriately in providing patient care.

The American Dental Society of Anesthesiology (ADSA) is accredited by the American Dental Association and Academy of General Dentistry to sponsor CE for dentists and will award CE credit for each article completed. You must answer 3 of the 4 questions correctly to receive credit.

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CE questions must be completed within 3 months and prior to the next issue.

1) According to the American Society of Anesthesiologists, which of the following preoperative adjuncts should be considered for patients with a higher risk of pulmonary aspiration and on GLP-1/GIP therapy?

   a. H_1 receptor antagonists (diphenhydramine)
   b. H_2 receptor antagonists (famotidine)
   c. Particulate antacids (magnesium or calcium carbonate)
   d. Selective-serotonin reuptake inhibitors (fluoxetine)

2) Which of the following therapies is indicated for patients unable to tolerate the gastrointestinal side effects of GLP-1 medications?

   a. Combination therapy of a GLP-1/GIP medication (tirzepatide) to lessen the side effects from a pure GLP-1 receptor agonist.
   b. Concurrent administration of a gastric motility drug (metoclopramide).
   c. Continuous co-administration of a particulate antacid to reduce the sequelae of eventual pulmonary aspiration.
   d. Immediate discontinuation of the GLP-1 medication and consideration of alternate therapies that include increased insulin and sulfonylurea dosing.

3) Glucose-dependent insulinotropic polypeptide (GIP) therapy produces all the following physiologic effects EXCEPT:

   a. delaying gastric emptying.
   b. increasing glucagon activity.
   c. regulating fat deposition.
   d. stimulating insulin production.

4) For patients taking a weekly dosed GLP-1 receptor agonist, what is the recommended modification to dosing prior to a scheduled, elective surgical procedures involving sedation or general anesthesia?

   a. No recommendation for withholding the GLP-1 receptor agonist therapy because of an increased risk of diabetic ketoacidosis.
   b. Withhold the GLP-1 receptor agonist therapy for at least 1 week prior to the scheduled procedure.
   c. Withhold the GLP-1 receptor agonist therapy for at least 2 months prior to the scheduled procedure and institute bridging therapy.
   d. Withhold the GLP-1 receptor agonist therapy for at least 24 hours prior to the scheduled procedure.