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To Hold or Not to Hold? Periprocedural Management of Glucagon-like Peptide-1 Receptor-based Agonists (GLP-1ra) in Patients with Diabetes and Obesity

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Glucagon-like peptide-1 receptor-based agonists have transformed the care of patients with diabetes and obesity. However, case reports that have associated their use with retained gastric contents and pulmonary aspiration have raised concerns regarding their safe use in patients undergoing procedures involving deep sedation, general anesthesia, or upper endoscopy. Here we present the evidence underlying these concerns and provide an evidence-informed framework for the periprocedural management of these agents. Further research is needed to better characterize these risks and provide mitigation strategies for individuals taking them in the perioperative period.

Introduction

Glucagon-like peptide-1 receptor (GLP-1r)-based agonists (GLP-1ra) were initially developed for the treatment of diabetes and obesity, but have since emerged as treatment options for a broader range of conditions, including obstructive sleep apnea, metabolic dysfunction associated steatotic liver disease, heart failure, chronic kidney disease, and even cardiovascular risk reduction in patients with obesity or diabetes.[1] Due to their myriad beneficial

Non GLP-1R-based agonists that can delay gastric emptying	• Opioid analgesics • Anticholinergic agents • Tricyclic antidepressants • Calcium channel blockers • Progesterone • Octreotide • Proton pump inhibitors • Interferon alpha • L-DOPA • Sucralfate • Aluminum hydroxide antacids • β-adrenergic receptor agonists • Glucagon

Figure 1. Non GLP-1ra medications that can delay gastric emptying.[11]

Abbreviations: GLP-1ra: Glucagon-like peptide-1 receptor-based agonists; **L-DOPA:** 3,4-dihydroxy-L-phenylalanine

effects, we have seen a surge in the prescription patterns for these medications,[2] one that is likely to continue with easier access and the growing number of indications for their use.

GLP-1ra have been associated with a delay in gastric emptying (GE), an effect that has been correlated with their antihyperglycemic and weight lowering effects.[3,4] This delay in GE, along with reports of retained gastric contents (RGC) and the risk of pulmonary aspiration, has raised concerns regarding their safety during the perioperative period. Recently, several international groups have provided guidance on the use of these agents prior to elective surgery. Considerable divergence exists within current guidance regarding perioperative treatment with these agents. Some groups have suggested withholding these agents in all patients for varying amounts of time, ranging from three drug half-lives,[5] to one day for daily and one week for weekly GLP-1ra.[6] Others advocate taking an individualized approach, withholding them in some patients deemed at higher risk for aspiration for one day for daily and one week for weekly GLP-1ra.[7] In contrast, several recommendations advise against withholding these agents prior to surgery.[8-10] Our own recommendations similarly support using a personalized approach to decisions regarding withholding these agents prior to surgery.[11] Here, we review the background underlying the risk of aspiration with the use of GLP-1ra in patients undergoing elective procedures involving deep sedation, general anesthesia, or upper endoscopy, and use this evidence to formulate recommendations for their use in this patient population.

GLP-1ra and Delayed Gastric Emptying

GE has been associated with diabetes, even without the use of GLP-1ra. Risk factors for its development include type 1 diabetes,[12] longstanding duration (>10 years) of diabetes,[13] poor glycemic control (HbA1c >9%),[14] and obesity.[15] GE delay has also been associated with other commonly prescribed medications, including opioid agonists, proton pump inhibitors, calcium channel blockers, tricyclic antidepressants, and non-prescription substances such as alcohol, tobacco, and nicotine (**Figure 1**).[16] Several symptom groups have been inconsistently associated with delayed GE, including early satiety, nausea, vomiting, dyspepsia, and bloating. While their absence does not exclude delayed GE, their presence often necessitates further investigations, treatments, and precautionary measures to avoid complications.

GLP-1ra affect the gastrointestinal motor neuron system by acting on receptors located on the myenteric neurons, leading to inhibition of peristalsis and delayed GE.[17] In a meta-analysis, this effect was associated with a 36-minute delay in GE for solids but not liquids; however, a high level of heterogeneity (I^2=79%) was observed among studies involving solids.[18] The degree of GE varies within the drug class, with more pronounced effects observed with short-acting agents (lixisenatide, exenatide) versus long-acting

GLP-1ra (liraglutide, dulaglutide, semaglutide).[19] Tirzepatide, a GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) co-agonist, has been shown to delay GE similar to that observed with GLP-1ra dulaglutide.[20] In a randomized, open label, head to head comparison, lixisenatide delayed GE to a greater extent compared to liraglutide.[21] Tachyphylaxis has been associated with longer acting, but not short-acting GLP-1ra. In studies examining the gastric emptying of solids in participants treated with liraglutide, GES time increased by 5 weeks of treatment, and decreased by 16 weeks, although it remained prolonged compared to baseline.[22] Similar results were reported in another trial with liraglutide, whereby liraglutide delayed GES at 5 weeks by a median of 70 minutes compared to placebo. While there was improvement in this parameter by 16 weeks, median GES time remained increased in those taking liraglutide by a median of 30 minutes compared to those taking placebo.[23] However, in half of these individuals who experienced GE delay at 5 weeks, it had normalized by 16 weeks, suggesting its reversibility in a subset of individuals taking liraglutide.[23] To our knowledge, data regarding the time to resolution of delayed GE upon discontinuing GLP-1ra are currently lacking.

GLP-1ra and Retained Gastric Contents

While there is evidence of a delay in GE with GLP-1ra which could be partially reversible with long-acting agents, it remains important to examine whether this delay leads to an increased risk of RGC. Multiple observational studies have demonstrated an increase in RGC on upper gastrointestinal endoscopy in individuals taking GLP-1ra compared to controls.[24-38] Evidence regarding whether holding GLP-1ra in accordance with multisociety guidance,[7] one day for daily agents and one week for weekly GLP-1ra, is mixed. Some studies suggest that withholding these agents protects against RGC with a reduction in this risk if these agents are withheld,[26] whereas others have demonstrated no difference in GLP-1ra cessation between those with and without RGC.[27] Potential mitigation strategies have also been explored that could be protective in reducing the risk of RGC, including use of a liquid diet on the day prior to same-day colonoscopy. In a case series of 57 individuals undergoing sleeve gastrectomy, no participant who adhered to a liquid diet for 24 hours prior to surgery experienced RGC.[35]

Contrary to this, a recent retrospective analysis reported a higher likelihood of RGC among patients taking GLP-1ra compared to those not taking these agents.[17] Among patients who underwent same-day colonoscopy, 86.4% were found to have RGC while only 13.6% did not. However, several limitations should be considered, including the retrospective nature of the study, the small number of patients who underwent same-day colonoscopy (n=22) versus the study population of 3,746 patients, the small number of patients on GLP-1ra (n=43), and the absence of information regarding concomitant use of medications or conditions that could affect gastric motility.

Diabetes itself could be a risk factor for RGC at the time of surgery, with or without the use of GLP-1ra. This possibility was evaluated in a meta-analysis that assessed RGC by ultrasonography and demonstrated a 2-fold higher prevalence of a “high-risk stomach” (increased antral cross-sectional area or gastric residual volume) in participants with diabetes mellitus. This study, however, did not specify the medication(s) used by these individuals and whether the use of GLP-1ra mediated this association.[39]

Another meta-analysis, which defined RGC as the finding of solid/food contents retained in the stomach assessed during gastroscopy, demonstrated a significantly higher risk among participants taking GLP-1ra compared to placebo (odds ratio [OR] 4.2).[40] While the duration of fast prior to the procedure did not appear to be protective against this risk,[41,42] most patients with RGC had been treated with a GLP-1ra for 2 months or less.[42,43] Although RGC was still experienced by some patients despite withholding the GLP-1ra for 7 days prior to the procedure,[44] the odds of RGC were higher in short term users (<12 weeks) versus long term users (>12 weeks) users of GLP-1ra (OR 2.48), providing credence to the view that the GLP-1ra-mediated effects on delayed GE may be partially reversible with long term use.[45]

GLP-1ra and the Risk of Aspiration

Although GLP-1ra have been linked with delayed gastric emptying of solids and the risk of RGC, let us turn our attention to the risk of aspiration in patients taking these agents prior to elective procedures. Much of the available data derives from observational studies with a high degree of heterogeneity. In many reported cases, pulmonary aspiration was experienced

by individuals who had received their last dose of GLP-1ra within one week prior to the procedure,[46,47] with treatment durations ranging from very recent use up to 20 weeks.[47,48] Notably, this timeframe corresponds to the dose escalation phase or the period shortly thereafter for weekly GLP-1ra. Despite these observations, the overall risk of pulmonary aspiration remains low. In a meta-analysis comprising 13 studies involving 84,065 patients, use of GLP-1ra was associated with elevated rates of RGC and aborted procedures, no significant differences in aspiration rates were found between those taking GLP-1ra and those who were not.[40] Findings from a separate meta-analysis of 13 studies yielded a non-significant increased risk of pulmonary aspiration with GLP-1ra treatment (OR 1.20), with at least moderate heterogeneity across studies (I^2=59%).[11] In contrast to these reports, a recent large retrospective database analysis identified that preoperative use of GLP-1 ra was associated with a lower risk of pneumonitis within 7 days post-surgery compared to non-use of these agents.[49] Among GLP-1 users, pneumonitis risk was increased in those with asthma, chronic obstructive pulmonary disease, and heart failure. Taken together, these data suggest that despite the delay in GE, and possibility of RGC, the risk of aspiration may not be universal in patients using GLP-1ra agonists in the perioperative period. These findings call for an individualized approach to preprocedural management rather than a universal strategy for withholding these agents.

Recommendations for Perioperative Management

Based on our understanding of the available data surrounding the risk of RGC and pulmonary aspiration associated with GLP-1ra, we suggest a personalized approach when deciding whether to withhold these agents prior to procedures involving deep sedation, general anesthesia, or upper endoscopy. These recommendations are consistent with our previously published guidance and are presented in **Figure 2**.[11]

1. All Individuals undergoing these procedures should follow standard fasting recommendations and adhere to a liquid diet for 8–12 hours prior to the procedure. The decision to withhold GLP-1ra should be individualized.
2. In most individuals, GLP-1ra therapy may not need to be routinely withheld prior to their procedure, since the risk of pulmonary aspiration remains low.
3. Individuals at higher risk of RGC or pulmonary aspiration, including those taking short-acting GLP-1ra; long-acting GLP-1ra initiated within the past 16 weeks, or currently undergoing dose titration; those experiencing ongoing gastrointestinal symptoms or diagnosed with gastroparesis; individuals with poor glycemic control (HbA1c >9%); or those taking other medications known to increase GE time (**Figure 1**), should have their GLP-1ra withheld.
4. If GLP-1ra is withheld, it should occur for >3 half-lives for weekly agents, and for >5 half-lives for daily agents (**Table 1**). In these cases, consideration should be given to bridging therapy for antihyperglycemic and anti-obesity effects.
5. In high-risk individuals who did not withhold their GLP-1ra prior to the procedure or have ongoing symptoms on the day of the procedure, or who require urgent procedures, point-of-care gastric ultrasound should be considered to assess for RGC. If ultrasound is unavailable, inconclusive, or reveals RGC, full stomach precautions should be implemented, or if possible, the procedure should be delayed.

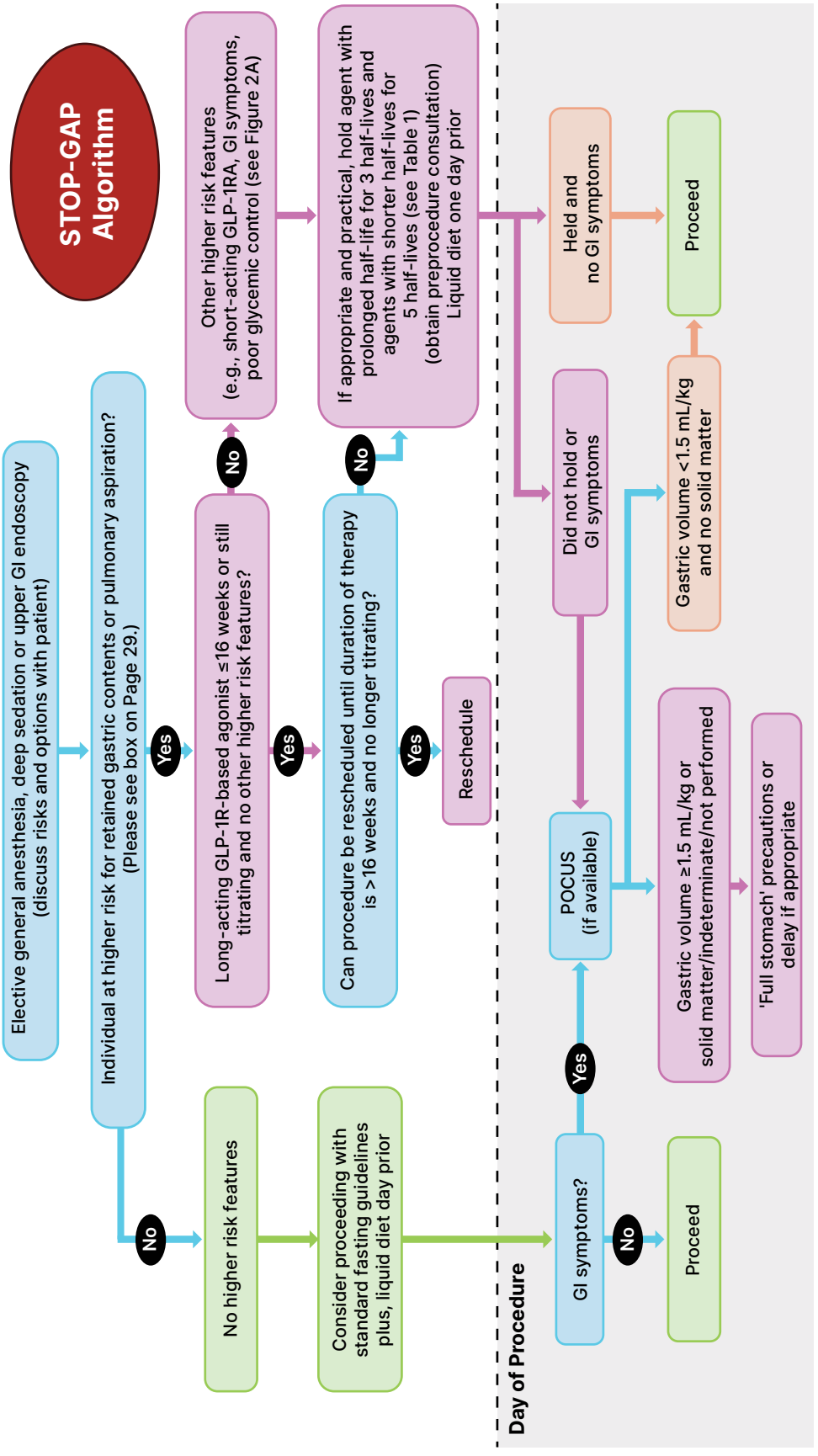


Figure 2. The STOP-GAP Algorithm.[11]

Abbreviations: GAP: GLP-ra related aspiration during procedures; **GI:** gastrointestinal; **POCUS:** point-of-care ultrasound.

Generic Name	Brand Name	Indications	Route and Frequency	Half-life	Cessation Time
Administered weekly (QW) or prolonged half-life					
Dulaglutide	Trulicity®	T2DM	SC QW	~5 days	~15 days[a]
Exenatide ER	Bydureon BCise®	T2DM	SC QW	~2 weeks	~6 weeks[a]
Semaglutide (injectable)	Ozempic®/Wegovy®	T2DM / Obesity	SC QW	~7 days	~21 days[a]
Semaglutide (oral)	Rybelsus®	T2DM	PO QD	~7 days	~21 days[a]
Tirzepatide	Mounjaro®/Zepbound®	T2DM / Obesity	SC QW	~5 days	~15 days[a]
Daily administered with shorter half-lives					
Exenatide IR	Byetta®	T2DM	SC BID	2.4 h	1 day[b]
Liraglutide[c]	Victoza®/Saxenda®	T2DM / Obesity	SC QD	13 h	3 days[b]
Lixisenatide[c]	Adlyxine	T2DM	SC QD	3.1 h	1 day[b]

Table 1. Half-lives and cessation times of GLP-1 receptor-based agonists.[11]

a: 3 half-lives;
b: 5 half-lives (rounded up to the nearest day);
c: also available as a fixed ratio combination (FRC) agent with basal insulin. If withholding an FRC agent, consider periprocedure use of the basal insulin component as per clinical judgement.

Abbreviations: BID: twice daily; **ER:** extended-release; **IR:** immediate-release; **PO:** per os (orally); **QD:** once daily; **QW:** once weekly; **SC:** subcutaneous; **T2DM:** type 2 diabetes mellitus.

Conclusion

GLP-1ra have transformed the treatment landscape for patients with type 2 diabetes and obesity. However, their use in the setting of procedures involving deep sedation, general anesthesia, or upper endoscopy have raised concerns about retained gastric contents and pulmonary aspiration. We provide an evidence-informed framework that emphasizes an individualized approach to decisions about preprocedural withholding of these agents. The current evidence, however, is based on observational studies with a high degree of heterogeneity. Well designed, prospective studies are required to further characterize this risk and elucidate the best strategies for risk mitigation.

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