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Editorial

EDITORIAL

# Perioperative management of long-acting glucagon-like peptide-1 (GLP-1) receptor agonists: concerns for delayed gastric emptying and pulmonary aspiration

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## Summary

Prescriptions and use of glucagon-like peptide-1 (GLP-1) receptor agonists are increasing dramatically, as indications are expanding from the treatment of diabetes mellitus to weight loss for people with obesity. As GLP-1 receptor agonists delay gastric emptying, perioperative healthcare practitioners could be concerned about an increased risk for pulmonary aspiration during general anaesthesia. We summarise relevant medical literature and provide evidence-based recommendations for perioperative care for people taking GLP-1 receptor agonists. GLP-1 receptor agonists delay gastric emptying; however, ongoing treatment attenuates this effect. The risk of aspiration during general anaesthesia is unknown. However, we advise caution in patients who recently commenced on GLP-1 receptor agonists. After over 12 weeks of treatment, standard fasting times likely suffice to manage the risk of pulmonary aspiration for most otherwise low-risk patients.

**Keywords:** diabetes mellitus; gastric emptying; glucagon-like peptide-1 receptor agonists; obesity; pulmonary aspiration

Current guidelines assign a Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) A recommendation for commencing a glucagon-like peptide-1 (GLP-1) receptor agonist as first-line therapy for the management of type 2 diabetes mellitus (T2D), particularly in people with obesity, atherosclerotic disease, or high cardiovascular risk.[1] In addition, long-acting GLP-1 receptor agonists are approved for the treatment of obesity independent of a diagnosis of diabetes mellitus.[2] Accordingly, the adoption of GLP-1 receptor agonists is increasing dramatically, and a growing number of people using GLP-1 receptor agonists require management in the perioperative setting.[3] One mechanism of GLP-1 therapy central to lowering glycaemia and weight loss is slowing gastric emptying.[4] This has raised concerns about increased gastric volumes and aspiration risk using traditional fasting times before anaesthesia. The American Society of Anesthesiologists recently published consensus-based guidance on the management of GLP-1 receptor agonists,[5]

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recommending holding once-daily dosed preparations 1 day and once-weekly dosages 1 week before elective surgery. This guidance is based on several recent case reports of pulmonary aspiration in patients using GLP-1 receptor agonists, yet lacks studies or discussion of the effects of GLP-1 therapy on gastric emptying. This scoping review summarises current evidence on the risks and benefits of GLP-1 receptor agonists in the perioperative setting to provide recommendations based on the best available evidence currently.

## Incretin therapies

Incretins are a group of hormones released by the intestines in response to oral intake, contributing to glycaemic homeostasis by stimulating pancreatic β cells to release insulin and inhibiting glucagon secretion from pancreatic α cells.[6] The main incretin hormones are GLP-1 and glucose-dependent insulinotropic peptide (GIP; also known as gastric inhibitory peptide). The effect of incretin hormones is glucose dependent,[7] therefore, incretin therapy is associated with a low risk of hypoglycaemia.[6] Dipeptidyl peptidase-4 (DPP-4) is a ubiquitous enzyme responsible for the degradation of GLP-1 and GIP, resulting in short half-lives of both hormones. The first commercial medications acting on the incretin system were DPP-4 inhibitors, which increased the effects of endogenous incretins. Subsequently, DPP-4-resistant analogues of GLP-1 were developed, with half-lives of several hours, compared with <5 min for endogenous GLP-1.[8] The newest GLP-1 receptor agonists, semaglutide and dulaglutide, have half-lives of several days with weekly dosing regimens. Most GLP-1 receptor agonists require subcutaneous injections, although an oral form of semaglutide is available.[9] Advances currently under investigation in clinical trials are dual and triple agonists, such as GLP-1/GIP, GLP-1/GLP-2, GLP-1/glucagon, and GLP-1/GIP/glucagon, with synergistic effects.[10–12]

The effectiveness of GLP-1 receptor agonists is well established in people with T2D, primarily lowering blood glucose levels and reducing body weight. In addition, GLP-1 receptor agonists carry beneficial cardiovascular effects. GLP-1 receptor agonists mitigate the risks of cardiovascular events such as acute myocardial infarction, stroke, and associated mortality.[13] A 7-year cohort follow-up study of high-risk patients managed with GLP-1 receptor agonists showed a 28% reduction in the incidence of major adverse cardiac events after adjusting for confounders (hazard ratio 0.72, 95% confidence interval 0.56–0.92).[14]

In addition to their glucose-lowering effects, the ability of GLP-1 receptor agonists to increase satiety and reduce oral intake results in marked weight loss and prevention of obesity-related complications.[15,16] GLP-1 receptor agonists have shown considerable efficacy in treating obesity, and thus have the potential to complement traditional interventions such as lifestyle modifications, behavioural programs, and bariatric surgery.[16] The recent SURMOUNT-1 and SURMOUNT-2 trials demonstrated significant, sustained weight loss within the confines of two phase 3 randomised placebo-controlled trials. These trials investigated the effects of a dual-acting GLP-1/GIP agonist (i.e. tirzepatide) in people with obesity without diabetes and in people with T2D.[17,18] Following the results of these trials, the indications for incretin therapies have expanded to the primary treatment of obesity regardless of T2D. Currently, semaglutide and liraglutide are approved for this indication in the USA, UK, and Europe.

## Incretins in the perioperative period

Data on the use of once-weekly GLP-1 receptor agonists in the perioperative setting are lacking; however, several studies with shorter-acting GLP-1 receptor agonists demonstrated effectiveness in improving glycaemic control and reducing insulin requirements in the perioperative period.[19] GLP-1 effectively reduced insulin requirements and lowered blood glucose in a randomised controlled trial in cardiac surgery patients.[20,21] A systematic review of GLP-1 therapy in the perioperative and critical care settings indicated that besides improved glycaemic control, the risk of hypoglycaemia is low,[22] making this an attractive alternative to insulin. This systematic review of (shorter-acting) incretin therapies in the perioperative period concluded that while only a few studies evaluated nausea and vomiting, they observed no increase in the incidence of nausea and vomiting with incretins compared with placebo.[22] To date, a few observational studies have assessed the incidence of residual gastric content (defined as any solids in the stomach or gastric volume >0.8 ml $kg^{-1}$) in GLP-1 receptor agonist users undergoing endoscopy.[23,24] Both studies found a significantly higher incidence of residual gastric content in patients using GLP-1 therapy (first study: 5.4% and second study: 24 %) compared with placebo (0.5% and 5.1%, respectively).[23,24] However, patients undergoing endoscopy are not entirely comparable with perioperative patients, and therefore, comprehensive data on the perioperative effects of incretin therapy on gastric emptying or the incidence of aspiration remain lacking.

## Effects of GLP-1 receptor agonists on gastric emptying

GLP-1 inhibits postprandial gastric emptying and reduces gastric acid secretion. Through the vagus nerve, GLP-1 suppresses gastric and duodenal peristalsis, elevating pyloric pressure. Gastrointestinal feedback mechanisms further reduce gastrointestinal motility and fluid secretion, resulting in feelings of satiety and limiting oral intake.[16] The effects of GLP-1 on gastric motility are considered subject to tolerance and tachyphylaxis, such that the effects are attenuated with ongoing treatment duration.[25,26] However, the study that introduced the concept of tachyphylaxis used continuous intravenous GLP-1 infusions, which are pharmacologically distinct from long-acting GLP-1 receptor agonists in current clinical use (i.e. duration of action, with up-titration of the dose at initiation of treatment). There is evidence that the prokinetic dosage of erythromycin (i.e. 200 mg) enhances gastric emptying in conjunction with the use of GLP-1 receptor agonists.[27] It is important to note that this study is limited by a small sample size and does not include people with obesity or T2D. While erythromycin use in patients with suspected (GLP-1-induced) delayed gastric emptying appears interesting, further research is needed to confirm its effectiveness, especially in people using GLP-1 receptor agonists for obesity or T2D management.

Aldawsari and colleagues[28] recently published a systematic review of all randomised trials studying the effects of GLP-1 treatment on gastric emptying in people with obesity. Two studies investigating liraglutide[29,30] reported delayed gastric emptying, while two studies using semaglutide[31,32] observed no significant delay. A notable difference between these studies was the duration of treatment of 6 weeks for the liraglutide studies compared with 12–20 weeks for the semaglutide studies.

This difference is relevant because 6 weeks is a relatively short and perhaps insufficient period to develop tachyphylaxis and tolerance. The four included studies[29–32] all used the paracetamol absorption test to assess gastric emptying. It is essential to highlight that, despite its widespread use, the paracetamol absorption test is widely recognised as a suboptimal method for measuring gastric emptying. While the approach is cost-effective, it poses limitations that undermine its reliability. It is imperative to acknowledge the necessity for more precise techniques, such as magnetic resonance imaging or scintigraphy, to measure gastric emptying and gain a comprehensive understanding of its intricate interactions with GLP-1 receptor agonists.[33] For now, in studies using the paracetamol absorption test, following an adequate duration for the development of tachyphylaxis and tolerance, and adherence to standard preoperative fasting periods exceeding 6 h, gastric emptying was similar to that seen before the initiation of GLP-1 receptor agonists.

Studies using scintigraphy provided similar results regarding gastric emptying with GLP-1 treatment. Although most studies confirm the delay in gastric emptying, gastric emptying was nearly complete or similar to baseline after a duration approaching perioperative fasting times (>6 h). A randomised controlled trial investigating the effects of once-daily liraglutide on gastric emptying using scintigraphy revealed a notable 25–40% delay in gastric emptying half-life after 8 weeks of treatment. Nevertheless, the percentage of the radiographic test dose excreted in individuals fasting for 4 h had nearly reverted to baseline.[34] Similarly, a study comparing 8 weeks of once-weekly exenatide with placebo revealed statistically increased gastric content after 120 min.[35] However, the reduction in gastric content followed a linear trajectory. Therefore, while a slight delay was noted, the effect seems to lack clinical significance in the context of a minimum fasting period of 6 h, as typically required for preoperative patients.

A recent retrospective study concluded that semaglutide was associated with decreased gastric emptying among patients undergoing upper endoscopy.[23] However, this study risked significant sources of bias. It included <50% of potentially eligible medical records, of which only 8% used a GLP-1 receptor agonist ($n$=33); besides, patients were unmatched and doses and durations of GLP-1 treatment were not reported. Considering these limitations, the clinical significance of this study is questionable.

In conclusion, we know that GLP-1 therapy can delay gastric emptying, most notably for the first postprandial hours and at the initiation of treatment. Crucially, this effect subsides as a result of tachyphylaxis following ongoing treatment. After 8–12 weeks, most studies observe a return to regular gastric emptying, similar to pre-intervention conditions, when adhering to perioperative fasting guidelines with durations exceeding 6 h.

## GLP-1 receptor agonists and risk of pulmonary aspiration

Although potentially highly consequential, perioperative pulmonary aspiration is a rare complication of anaesthesia, with an incidence of approximately one per 3000–7000 elective surgery cases.[36,37] With the increasing use of GLP-1 receptor agonists in the perioperative period, clinicians should be aware of a '*post hoc* ergo propter hoc fallacy'. Recently, several case reports have reported perioperative pulmonary aspiration in patients using long-acting GLP-1 receptor agonists.[38] Further, there are reports of increased fasting gastric contents in patients using these medications.[39] The authors suggest that GLP-1 receptor agonists might be implicated in the risk of pulmonary aspiration and question whether physicians should discontinue these medications preoperatively. Increasingly, people with T2D and obesity receive GLP-1 receptor agonist prescriptions, and hence, it is also expected that aspiration events will occur in patients with T2D or obesity using GLP-1 receptor agonists. These reports have little informative value regarding the causal aspiration risk associated with GLP-1 use and emphasise the need for an unbiased prospective cohort study.

Given the rarity of pulmonary aspiration, demonstrating the safety of any intervention targeting this complication requires an enormously large sample size. In the absence of definitive evidence, we must assess the advantages and disadvantages of continuing GLP-1 receptor agonists preoperatively *vs* discontinuing them.

## Recommendations

1. **Exercise caution with short-term GLP-1 receptor treatment duration**
   The impact of shorter-term incretin use on the risk of aspiration following regular preoperative fasting remains uncertain because of the absence of robust data. After long-term use of incretins (i.e. ≥12 weeks), gastric emptying appears to normalise as a result of tachyphylaxis. For shorter durations of treatment, practitioners should exercise careful clinical judgment, especially in the context of persistent gastrointestinal symptoms.[23] Of note, it is unknown how long GLP-1 receptor agonists require withholding to normalise gastric emptying.
2. **Assess perioperative risk for people with T2D regarding continuation or cessation of incretin treatment**
   People with T2D can experience delayed gastric emptying and a subsequent risk of aspiration, irrespective of incretin treatment. The impact of incretin therapy on exacerbating this risk remains unestablished. Weighing the benefits of ongoing treatment against the potential perioperative drawbacks becomes pivotal, especially for the longer-acting, weekly GLP-1 receptor agonists. Pharmacokinetically, drug clearance requires 4–5 half-lives, resulting in cessation of therapy of several weeks. Such discontinuation could compromise glycaemic control during this period, which is linked to adverse postoperative outcomes[40] and should be weighed against the risk of aspiration on an individual basis.
3. **Consider using erythromycin in patients at a high risk of pulmonary aspiration**
   Erythromycin's ability to counterbalance GLP-1-induced gastric emptying delay could offer a strategy for mitigating the risk of pulmonary aspiration. Erythromycin's definitive benefits, when weighed against potential side-effects, are yet to be established, and further evaluation of its effectiveness in this context is warranted. Therefore, its consideration is most justified in the highest-risk populations for pulmonary aspiration.

4. **Perform comparative studies on gastric volumes**
   Subsequent research endeavours should undertake comparative analyses to contrast perioperative gastric volumes between people with obesity and T2D using GLP-1 receptor agonists and untreated counterparts with matching characteristics. Given the relative rarity of pulmonary aspiration, studies in this domain demand substantial sample sizes for thorough exploration. Preoperative gastric ultrasound could serve as a proxy for the risk of aspiration, enabling smaller prospective studies.

## Conclusions

People who have started incretin therapy within 8–12 weeks before surgery could be at risk of delayed gastric emptying, but evidence of risk for aspiration during the perioperative period is currently lacking. In addition, there are no data on the more recent combination preparations. Thus, anaesthesiologists should be aware of the possibility of delayed gastric emptying for people who have started GLP-1 receptor agonists in the last 8–12 weeks and make a risk–benefit analysis concerning perioperative measures.

## Authors' contributions

Drafting of the initial manuscript: MLvZ and AHH.
Critically revising the manuscript for important intellectual content: SES, MPP, AMD, JH.
Approving the final version and being accountable for all aspects of the work: all authors.

## Declaration of interest

The authors declare that they have no conflicts of interest.

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