

GLP-1 Receptor Agonists - An Anaesthesiologist's Perspective – A Comprehensive Review

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INTRODUCTION

GLP-1 receptor agonists help in regulating blood sugar levels and encouraging weight reduction in individuals with non-insulin-dependent diabetes mellitus who adhere to dietary guidelines and exercise regularly. Semaglutide is a commonly utilized type of GLP-1 receptor agonist. The injection is usually administered once every seven days subcutaneously, beginning at 0.25 mg, with the highest weekly dosage is between 2.0 and 2.4 mg (larger doses are employed to promote weight loss instead of regulating blood sugar). Semaglutide's half-life is approximately one week, indicating it remains active in the body for a long duration. So, it requires roughly five weeks to reach its stable level in the body, and it also takes the same amount of time for its effects to cease after discontinuation. There is now an oral formulation, and its effects might resemble those of the injection (1,2)

There has been significant expansion in GLP-1 receptor agonists in North America. For instance, after receiving approval from the Food and Drug Administration in the USA in 2017, semaglutide is now frequently employed to manage diabetes and help with weight loss, semaglutide has two brand names, Wegovy (novoMEDLINK™, a division of Novo Nordisk A/S located in Denmark, Ozempic (Novo Nordisk A/S, located in Denmark), often featured on TV news and popular social media sites. It's approximated that nearly five million prescriptions for semaglutide were filled in the USA alone in 2020. The count is likely much higher by now. (2,3)

BACKGROUND

GLP-1 receptor agonists work by replicating the actions of the natural hormone GLP-1. Activating the GLP-1 receptor lowers blood glucose by prompting the body to secrete less glucagon and more insulin. Moreover, in larger amounts, GLP-1 receptor agonists reduce hunger and promote weight loss by affecting the hunger centres in the brain and slowing down the emptying of the stomach 2 — But we're still figuring out the specific impact of these two actions. This could also be the reason why many individuals who take

GLP-1 receptor agonists commonly complain of feeling vomiting and nausea. (2, 4, 5)

Considering the health of a whole population, GLP-1 receptor agonists look like they might have significant health outcomes, especially due to the widespread challenges posed by type 2 diabetes and obesity in our society. (6) However, even medications that are effective for some individuals might need to be discontinued or modified to safely manage the time around surgery. Some typical examples consist of warfarin, angiotensin-II receptor blockers, insulin and clopidogrel (2)

Presently, there haven't been any investigations that particularly examined whether GLP-1 receptor agonists are medically beneficial or safe in the perioperative setting. However, theoretically, GLP-1 receptor agonists may cause a delay in stomach emptying (7,8) which could be harmful for patients undergoing surgery because it increases the risk of aspirating regurgitated stomach material.

Recent data suggests that using GLP-1 receptor agonists during surgery might not be safe, particularly with a potentially increased frequency of stomach contents regurgitating and being aspirated into the lungs. During March 2023, the Journal made accessible online before printing what we discern as the initial depiction of inhaling stomach contents in an individual utilizing semaglutide for weight reduction, where a distinct and compelling correlation between the medication and subsequent aspiration during monitored anaesthesia was recommended for an upper gastrointestinal endoscopic procedure (Despite fasting appropriately for 18 hours). During June 2023, the journal released another case study involving a patient (lacking diabetes or obesity, had abstained from solid foods for around 20 hours and water clear liquids for around 8 hours) during elective breast surgery under general anaesthesia, the individual regurgitated a significant amount of stomach contents but propitiously did not inhale. These two case studies are featured within the current edition of the journal. (6).

Moreover, in this month's journal issue emphasizing a specific focus on gastric ultrasound – Sherwin et al. discuss

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the outcomes of a small research study focused on adult participants who had fasted—ten using semaglutide and ten control volunteers not using semaglutide (9) Given the positioning of the volunteer during the ultrasound technique, the likelihood of having undigested matter in the stomach, in contrast to the control group, varied from 3.5 to 7.4 times. In this investigation, as high as 90% of individuals using semaglutide (while only 20% of controls) displayed evidence of undigested food in the stomach. While not definitive and subject to significant constraints, this early investigation provides proof of delayed stomach emptying in fasting volunteers who are using semaglutide. (2)

Certainly, case reports and reviewing past observations along with discussions among physicians worldwide and sporadic tweets) have a restricted capability to directly influence clinical management. These might just be coincidental associations, and there may not be a direct cause-and-effect association between GLP-1 receptor agonists and either inhaling stomach contents or regurgitation of stomach contents. However, initial signs of safety concerns with new medicines could reasonably arise from physicians' recorded observations documented as case studies, later studied for links through observational investigations. When these initial problem manifest, particularly when the potential negative effects have life-threatening risks to individuals, it becomes logical to adhere to the precautionary measure. After combining this measure with the recent indication of concern, instead of presuming GLP-1 receptor agonists are harmless before surgery, it's better to assume they could be risky and proceed with caution (Until more data is obtained and the actual issue—or its absence—is better illuminated.). (2)

Studies show that it's important to be careful and consider these things for individuals taking GLP-1 receptor agonists prior to surgery:

1. If you're using GLP-1 receptor agonists for weight loss, consider discontinuing the medication for approximately three half-lives (around 88% of the drug is cleared from the body), prior to the scheduled procedure or surgery. For semaglutide, this involves a three-week period

For individuals using GLP-1 receptor agonists for diabetes mellitus (type 2): consider discussing with an endocrinologist about whether it's a good decision to discontinue the medication for approximately three half-lives before the planned medical procedure.

2. There's probably no need for individuals using GLP-1 receptor agonists to prolong their fasting period due to the harmful effects of fasting before surgery (10) and the research evidence available doesn't show a safe fasting period for these patients.

3. If it's not possible to discontinue GLP-1 receptor agonists for a minimum of three half-lives, evaluate the option of performing rapid sequence induction if you require general anaesthesia to reduce the risk of inhaling stomach contents. When general anaesthesia isn't considered (such as with

monitored anaesthesia care), medical providers must understand the elevated risk of regurgitation of stomach contents. This acknowledgment may result in the provider to employ a cuffed endotracheal tube for the management of airways during general anaesthesia following a rapid sequence induction, instead of administering the originally intended sedation. Other strategies for risk mitigation are available, Other strategies for risk mitigation are available, such as the utilization of prokinetic drugs like metoclopramide.

4. Contemplate using point-of-care gastric ultrasound for the assessment of composition and volume of any remaining contents within the stomach (but it is crucial to recognize the potential for false negative and false positive results with this technique (11)

5. Urgent investigation is needed, through well-conducted, sufficiently powered research to examine the safety profile of GLP-1 receptor agonists in the perioperative stage needs additional scrutiny.

6. According to shared decision-making principles, it is imperative to engage in open and transparent discussions with the patient regarding all the above factors, with a clear insight into the advantages and risks of each option.

The American Society of Anaesthesiologists (ASA) also reviewed information about GLP-1 agonists and their GI - related side effects, this involves studying the outcomes of delayed gastric emptying. There are only a few case reports that provide advice on how to manage these drugs prior to surgery to prevent respiratory difficulties and regurgitation. However, considering the concerns about GLP-1 agonists leading to delayed stomach emptying and the elevated risk of regurgitation of stomach contents, the ASA task force recommends the following for scheduled procedures. When patients require emergency or urgent procedures, manage them as if they have full stomach and address the situation accordingly. (12, 13)

If patients are scheduled for elective surgeries, consider the following below:

Day(s) before the Procedure:

1. For patients taking their medication daily, consider discontinuing GLP-1 agonists on the day of surgery or procedure.
2. For patients taking their medication weekly, consider discontinuing GLP-1 agonists a week prior to surgery or procedure

A number of regularly used GLP-1 receptor agonists, their indications and half-lives are given in the table below (14, 15, 16,17, 18, 19)

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Generic name	Brand name	Indications	Half-lives
Semaglutide	Ozempic/wegovy	T2DM/obesity	6-7 days
Dulaglutide	Trulicity	T2DM	5 days
Liraglutide	Saxenda/ Victoza	T2DM/Obesity	11-15 hours
Exenatide (extended release)	Bydureon Bcise	T2DM	8-16 days
Lixisenatide	Adlyzin	T2DM	3-5 hours

This recommendation is consistent, whether it's for weight loss or for type 2 diabetes, regardless of the type of procedure/surgery. You discontinue GLP-1 agonists for diabetes for an extended period, consider seeking assistance on managing diabetes and consider bridging treatment to treat diabetes with Insulin.

If the GLP-1 agonists were discontinued as instructed, continue as usual. If the patient shows no signs of stomach disorders, but the GLP-1 agonists weren't discontinued as recommended, proceed cautiously as 'full stomach' or consider evaluating stomach volume utilizing ultrasound if feasible and if experienced in the technique. If the stomach is devoid of contents, continue with usual procedures. If the gastric antrum volume is full or if there is uncertainty regarding gastric ultrasound results, consider postponing the procedure or treating the individual as if they have a 'full stomach' and consider inserting a oro-gastric tube to suction the stomach contents. Address and discuss the possible risks of pulmonary aspiration and regurgitation of stomach contents with the patient and the surgeon (12, 14).

There's no indication to indicate the ideal fasting duration for patients using GLP-1 agonists. Hence, until we have adequate evidence, we recommend complying with the current ASA fasting standards.

Currently, the optimal strategy for managing these patients requires further refinement, and it is anticipated that further investigations will assist in shaping our decision-making. Utilizing a systematic strategy to evaluate risk in this population, encompassing a meticulous examination of comorbidities, symptoms and medication history, is crucial. It might be advisable to reconsider conventional fasting protocols in this patient demographic. The application of gastric ultrasound to assess gastric contents before using anaesthesia could be an option for these patients presenting for anaesthesia.

In situations marked by uncertainty about gastric contents, the consideration of anaesthesia's rapid sequence induction and gastric decompression before emergence might be considered appropriate. It is crucial to acknowledge that the risk of aspiration and vomiting during emergence persists as a significant concern, even following gastric decompression. (2, 12)

CONCLUSION

GLP-1 receptor agonists help in regulating blood sugar levels and encouraging weight reduction in individuals with non-insulin-dependent diabetes mellitus. We understand the

complexity of ascertaining the exact cause of delayed gastric emptying in patient as there are various risk factors. However, with the increasing prevalence of GLP-1 receptor agonist administration, anaesthesiologists must familiarize themselves with these specific medications and the possible risks they might pose to individuals undergoing anaesthesia. Additional investigations examining the safety profile of these particular agents in the peri-anaesthetic duration is warranted.

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