Considerations of delayed gastric emptying with peri-operative use of glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs), such as semaglutide, dulaglutide and liraglutide, augment glucose-dependent β-cell insulin release, suppress glucagon secretion, and slow gastric emptying. In Australia, they are available as daily (liraglutide) or weekly (dulaglutide, semaglutide) subcutaneous injections; internationally, semaglutide is also available in a daily oral preparation. GLP-1 RAs have increased in popularity in recent years due to their potent effect on glycaemia and adiposity, as well as their cardiovascular benefits in patients with type 2 diabetes.[1-3]

There has been increasing interest in the use of GLP-1 RAs at higher doses for the management of obesity.[4] The combination of a GLP-1 RA with a glucose-dependent insulinotropic polypeptide RA as tirzepatide led to > 20% weight loss in the majority of clinical trial participants with and without diabetes.[5,6] The use of these medications is likely to increase, and possible adverse events should be highlighted. The most commonly reported side effects of GLP-1 RAs are gastrointestinal, specifically nausea and vomiting.[1-3] An emerging possible adverse event related to the effects of GLP-1 RAs on gastric emptying is aspiration during anaesthetic, regardless of best management.

Few large studies have assessed the effects of GLP-1 RAs on gastric emptying, and questions remain regarding the methodologies used to measure it.[7] The effects of GLP-1 and GLP-1 RAs on gastric emptying are purported to differ between short- and long-acting formulations. In a small Japanese study, short-acting lixisenatide delayed gastric emptying, whereas liraglutide and dulaglutide did not.[8] However, the doses of the longer acting formulations used in this study were lower than those currently available in Australia (liraglutide 0.9 mg daily and dulaglutide 0.75 mg weekly). In a randomised trial comparing short-acting lixisenatide (20 µg daily) and liraglutide (1.2 mg and 1.8 mg daily), both in combination with insulin glargine, lixisenatide markedly delayed gastric emptying and lowered post prandial glucose levels.[9] Although it has also been suggested that the effect of GLP-1 RAs on gastric emptying may lessen with prolonged exposure, there is limited evidence to support this. Small studies of GLP-1 infusions demonstrated rapid tachyphylaxis for up to 24 hours.[10,11]

Although there have been a number of studies assessing the use of GLP-1 RAs in the peri-operative period, few have assessed gastrointestinal effects such as nausea or gastric emptying.[12] The benefits of tight glycaemic control in the peri-operative period, particularly in relation to post-operative infection, have supported the use and continuation of GLP-1 RAs in patients with type 2 diabetes undergoing surgery.[13,14]

In the studies that did assess nausea, there did not appear to be an increase in post-operative nausea with GLP-1 RA use.[13,14]

We recently reported two cases of retained gastric contents with use of GLP-1 RAs before gastroscopy.[15] Additionally, a matched pair case–control study of 205 pairs with diabetes undergoing oesophagogastroduodenoscopy found increased rates of retained solid gastric residue with GLP-1 RA use (5.4% *v* 0.5%).[16] Similarly, a single-centre retrospective audit of 404 oesophagogastroduodenoscopy patients found higher rates of retained solid gastric contents or > 0.8 mL/kg retained fluid content in patients exposed to semaglutide ($n = 33$) in the 30 days before the procedure compared with those not exposed (24.2% *v* 5.1%, respectively).[17] The presence of gastrointestinal symptoms in the 24 hours before the procedure was associated with retained gastric contents. Interestingly, the mean time since last dose of semaglutide was ten days, and one patient in the semaglutide group developed pulmonary aspiration.[17] In a case report, retained gastric contents were associated with pulmonary aspiration in the presence of semaglutide initiation two months previously.[18]

Until recently, many position statements and review articles had suggested not withholding GLP-1 RAs pre-operatively in patients with type 2 diabetes, unless post-operative pancreatitis or ileus was present.[19,20] In its consensus-based guidance on pre-operative management of patients receiving GLP-1 RAs, the American Society of Anesthesiologists suggested that patients treated with GLP-1 RAs who require urgent surgery should be treated as though they have a full stomach, with appropriate airway protection.[21] In patients undergoing elective surgery, it recommends that the GLP-1 RA be withheld for one dose (either the day or week of surgery, depending on formulation) and the presence of gastrointestinal symptoms should be considered when assessing risk.[21] The statement highlights that there is insufficient evidence to suggest the optimal duration of fasting for patients exposed to GLP-1 RAs. Subsequently, and in contrast, several American gastroenterology associations, societies and the American College of Gastroenterology released a multi-society statement that there is little or no data about the risk of aspiration and that the impact of stopping GLP-1 RAs is unknown.[22] Hence, they did not make any direct recommendation and suggested to exercise best practice until more data are available.

Although GLP-1 RAs were initially marketed for management of type 2 diabetes, their approved (liraglutide) and off-label (semaglutide, dulaglutide) use in Australia for weight management has increased. Despite this increase in use outside of type 2 diabetes, there has not been a clear distinction in how to

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approach the peri-operative period in patients without diabetes receiving GLP-1 RAs. In patients with type 2 diabetes, the glycaemic benefit of these agents in the peri-operative period is likely to outweigh potential issues related to delayed gastric emptying and peri-operative nausea. However, when a GLP-1 RA is used to induce weight loss in patients without diabetes, the risks may outweigh the benefits. When a GLP-1 RA is used intermittently in patients without diabetes, the effects on delayed gastric emptying may be more pronounced, due to lack of the tachyphylaxis effect. Additionally, higher GLP-1 RA doses are used for weight management, and older exploratory studies found that higher doses of GLP-1 infusion (1.2 pmol/kg/min) were associated with near complete gastric stasis.[23]

While GLP-1 RAs should be considered an independent risk factor for retention of gastric contents in fasted individuals, comorbidities and co-prescribed medications may also contribute. Indeed, diabetes itself is associated with delayed gastric emptying.[24] Commonly co-prescribed medications that affect gastric emptying peri-operatively include opioids and proton pump inhibitors (Box).[25] We propose that if patients are treated with additional drugs that slow gastric emptying, further consideration of this risk should be accounted for when deciding fasting time and airway support.

The current literature focuses on gastroscopy, where the gastric contents can be directly viewed. The risk of aspiration from stomach contents may also be relevant to other procedures and may be underappreciated as the stomach is not visualised. The risk of aspiration with GLP-1 RAs is potentially lower in patients undergoing colonoscopy, owing to the prolonged fast required to clear the colon.[17]

In conclusion, GLP-1 RAs delay gastric emptying, with the potential risk of aspiration with peri-operative use. In patients treated with GLP-1 RAs and additional medications that delay gastric emptying, or in patients with gastrointestinal symptoms, the risk of aspiration is likely higher. Given the long half-life of the weekly preparations, it is likely that withholding semaglutide or dulaglutide for one week will be insufficient to prevent the effects on gastric emptying. A longer cessation time, combined with prolonged fasting, may be required. In the absence of evidence, a 24-hour clear fluid regimen could be considered regardless of the procedure or anaesthetic technique planned, especially if the GLP-1 RA has recently been commenced. Further research is required to assess the peri-operative risks of GLP-1 RAs, particularly in patients without type 2 diabetes and in other procedures requiring anaesthetic.

Medications and substances that can delay gastric emptying

Prescribed medications

- Glucagon-like peptide-1 receptor agonists
- Opioid analgesics
- Anticholinergic agents
- Tricyclic antidepressants
- Calcium channel blockers
- Progesterone
- Octreotide
- Proton pump inhibitors
- H_2-receptor antagonists
- Interferon alfa
- L-dopa
- Sucralfate
- Aluminium hydroxide antacids
- β-adrenergic receptor agonists
- Glucagon
- Calcitonin
- Dexfenfluramine
- Diphenhydramine

Non-prescribed substances

- Alcohol
- Tobacco/nicotine
- Tetrahydrocannabinol

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