Clinical Practice Recommendation On Periprocedural Use Of GLP-1/GIP Receptor Agonists

A consensus clinical practice recommendation endorsed by the Australian Diabetes Society (ADS), National Association of Clinical Obesity Services (NACOS), Gastroenterological Society of Australia (GESA) and Australian and New Zealand College of Anaesthetists (ANZCA).

Purpose of this document

In response to recent case reports of retained gastric contents and pulmonary aspiration during sedation for endoscopic procedures or general anaesthesia in people with diabetes and/or obesity treated with GLP-1 receptors agonists (GLP-1RAs), a clinical practice recommendation regarding the periprocedural use of GLP-1RAs/GIP Receptor Agonists (GIPRAs) has been co-authored by representatives from the Australian Diabetes Society (ADS), National Association of Clinical Obesity Services (NACOS), Gastroenterological Society of Australia (GESA) and Australian and New Zealand College of Anaesthetists (ANZCA). The below represents a consensus based on review of currently available evidence and consensus expert opinion. Although the current level of evidence is weak to inform a guideline, this document was written to mitigate the risk of pulmonary aspiration with the periprocedural use of GLP-1RAs/GIPRAs which, although rare, is potentially fatal.

Clinical Practice Recommendation Regarding Use Of GLP-1 Receptor Agonists and Dual GLP-1 and GIP Receptor Co-agonists **Prior to Endoscopic Procedures**

As these recommendations are based on expert opinion, they should not replace clinical judgement.

1. Patients should be asked about the use of GLP-1RA and GLP-1/GIPRAs prior to undergoing endoscopic procedures.
2. There are insufficient data at this time to support the omission of GLP-1RA and GLP-1/GIPRAs prior to endoscopy.
3. All patients taking GLP-1RA and GLP-1/GIPRAs within 4 weeks preceding an elective upper endoscopic procedure should follow a fluid diet for 24 hours prior to endoscopy.
4. All patients taking GLP-1RA and GLP-1/GIPRAs within 4 weeks preceding colonoscopy should undergo routine preparation according to local practice.
5. If there are clinical concerns that retained gastric contents may be present, consider a topical anesthesia approach [11, 12] minimally sedated gastroscopy (with an ultrathin 5 mm gastroscope if available) to inspect the stomach. If any solid intra-gastric contents are present, the endoscopic procedure (s) should be abandoned.
6. If retained gastric contents are present on gastroscopy, planned synchronous colonoscopy should be reconsidered or performed minimally sedated with appropriate precaution including availability of appropriate equipment for mouth suction or following rapid-sequence induction general anaesthesia to ensure airway protection.

7. If an emergency or urgent endoscopic procedure is required for a patient treated with GLP-1RA and GLP-1/GIPRAs, consider seeking support from an anaesthetist and the use of erythromycin (in the absence of contraindications) prior to the endoscopic procedure to accelerate gastric emptying. A single dose of 3mg/kg (up to a dose of 250mg) erythromycin intravenously has been shown to accelerate gastric emptying within 15 minutes [2-9]. We recommend a longer duration of 1-2 hours between administration of erythromycin and endoscopy when possible. Acute hyperglycaemia has the potential to attenuate the acceleration of gastric emptying by iv erythromycin [10].
8. As these recommendations are based on expert opinion, they should not replace clinical judgement.

Given the uncertainty of the evidence and knowledge base surrounding GLP-1 agonists in the perioperative period, these guidelines will be reviewed in December 2024.

Clinical Practice Recommendation Regarding Use Of GLP-1 Receptor Agonists and Dual GLP-1 and GIP Receptor Co-agonists **Prior to Anaesthesia for Non-Endoscopic Procedures**

As these recommendations are based on expert opinion, they should not replace clinical judgement.

1. Patients should be asked about the use of GLP-1RA and GLP-1/GIPRAs prior to undergoing anaesthesia. The patient should be involved with discussions regarding planning for the procedure, including risks and benefits of withholding therapy and those of alternative and mitigating strategies.
2. At this time, there are insufficient data to support the cessation of GLP-1RA and GLP-1/GIPRAs prior to anaesthesia, but it is reasonable to omit liraglutide (once-daily GLP-1RA) on the day of the procedure. Omission of longer-acting GLP-1RA and GLP-1/GIPRAs for an extended duration may delay urgent surgery or lead to poor glycaemic control at the time of surgery with consequent risks of increased morbidity, length of stay and potentially further deceleration of gastric emptying resulting from hyperglycaemia. The duration of inhibition of gastric emptying from longer acting GLP-1RA and GLP-1/GIPRAs is unknown and may potentially be several weeks.
3. All patients taking GLP-1RA and GLP-1/GIPRAs within 4 weeks preceding anaesthesia should be considered non-fasted/to have a full stomach and anaesthesia should be administered according to local practices for a non-fasted patient. Appropriate anaesthetic techniques should be applied to protect against pulmonary aspiration. Without being prescriptive, consideration should be given to regional anaesthetic techniques with minimal sedation and maintenance of upper airways reflexes, or rapid sequence induction for patients requiring general anaesthesia.
4. If bedside point-of-care gastric ultrasound and the necessary expertise are available, ultrasound may be used for risk stratification to determine the qualitative and quantitative content of the stomach prior to anaesthesia [1]. The absence of gastrointestinal symptoms does not exclude significant retention of gastric contents and should not be used to risk stratify patients. Conversely, the presence of gastrointestinal symptoms may be associated with increased risk.
5. Extending the fasting time is not recommended given the current lack of evidence that prolonged fasting reduces the risk of retained gastric contents.
6. It is reasonable to consider the use of iv erythromycin (in the absence of contraindications) prior to anaesthesia to accelerate gastric emptying. A single dose of 3mg/kg (up to a dose of 250mg) erythromycin intravenously has been shown to accelerate gastric emptying markedly within 15 minutes [2-9]. We recommend a longer duration of 1-2 hours between administration and induction of anaesthesia when possible. Acute hyperglycaemia has the potential to attenuate the acceleration of gastric emptying by iv erythromycin [10].
7. As these recommendations are based on expert opinion, they should not replace clinical judgement.

Given the uncertainty of the evidence and knowledge base surrounding GLP-1 agonists in the perioperative period, these guidelines will be reviewed in December 2024.

Background

Endogenous glucagon-like peptide-1 (GLP-1) and gastric emptying

Endogenous GLP-1 regulates post-prandial blood glucose levels by augmenting glucose-dependent insulin release, by suppressing glucagon secretion and by slowing gastric emptying. The latter delays the entry of nutrients into the small intestine and, thereby, their absorption. Changes in small intestinal transit/motility (which has been much less studied than gastric emptying) are also likely to contribute to glucose lowering by GLP-1 [13]. In healthy volunteers [14-17] and individuals with type 2 diabetes [18], intravenous infusion of GLP-1, even in modestly supraphysiological concentrations, slows gastric emptying. The magnitude of this delay, while variable, is often substantial. Intravenous infusion of the specific GLP-1 antagonist, exendin (9-39), accelerates gastric emptying in health, consistent with the concept that GLP-1 acts as a physiological modulator of gastric emptying [19]. Accordingly, the effect of exogenous GLP-1 to slow gastric emptying significantly is not surprising. In healthy individuals, exogenous administration of GLP-1 induces relaxation of the proximal stomach, which together with the stimulation of pyloric contractility and suppression of antral contractility, is likely to contribute to the slowing of gastric emptying [16]. However, in individuals with diabetes and cardio-vagal dysfunction the relaxation of the proximal stomach by GLP-1 is attenuated or absent [20]. With sustained exposure (e.g. intravenous infusion for 24 hours) the effect of GLP-1 to slow gastric emptying in healthy subjects is diminished i.e. there is evidence of tachyphylaxis. However, the magnitude of the slowing remains substantial [21].

GLP-1 receptor agonists and gastric emptying

GLP-1 receptor agonists (GLP-1RAs) have been developed as treatments for type 2 diabetes and obesity. They are now used widely and increasingly (Table 1). GLP-1RAs can be classified as shorter-acting or longer-acting based on their plasma half-life, with shorter-acting GLP-1RAs dosed once or twice daily and the majority of long-acting GLP-1 RAs dosed weekly. The shorter-acting GLP-1RAs, exenatide twice daily and lixisenatide (which have been used extensively, but neither of which are available for clinical use in Australia), slow gastric emptying markedly in both healthy subjects [22-24] and individuals with type 2 diabetes [23-30].-In the latter group the magnitude of this slowing is also predictive of the reduction in postprandial glucose [25, 28]. It is not widely appreciated that the slowing of gastric emptying by shorter-acting GLP-1RAs occurs with doses substantially less than those used for glucose-lowering in type 2 diabetes [24, 25]. Small intestinal transit is also inhibited by intravenous infusion of exenatide in healthy subjects and people with type 2 diabetes, associated with reductions in duodenal pressure waves and antegrade flow events [31]. Exenatide twice daily has been evaluated in a small study of individuals with type 2 diabetes with and without gastroparesis, with slowing of gastric emptying evident in all those without gastroparesis (20 of 20 individuals) and in only 2 of 10 individuals with pre-existing gastroparesis [32]. This observation and the outcomes of other studies [25, 28] indicate that the degree of slowing of gastric emptying observed with shorter-acting GLP-1RAs is proportional to the baseline rate of gastric emptying, with little, if any, further slowing in those with abnormally delayed emptying. This may be of particular importance - while approximately 30% of individuals with longstanding, poorly controlled diabetes have gastroparesis [33], in both well-controlled type 2 diabetes and obesity it is now appreciated that gastric emptying is frequently accelerated [34, 35].

The longer-acting GLP-1RAs, liraglutide, dulaglutide, exenatide once weekly (QW) and semaglutide (subcutaneous and oral) have for the main part had their effect on gastric emptying evaluated using the paracetamol absorption test, a suboptimal methodology [36-39]. It has been widely assumed that longer-acting GLP-1RAs do not slow gastric emptying with sustained administration because of tachyphylaxis. Rather, the three longer-acting GLP-1RAs that have been assessed using scintigraphy, the 'gold-standard' method for quantifying gastric emptying - liraglutide [40, 41], exenatide QW [42] and semaglutide sc (1.0 mg/wk) [43] – have been shown to slow gastric emptying with sustained administration. An 8-week study of exenatide QW resulted in a substantial delay in gastric emptying of both solids and liquids in healthy subjects [42]. Similarly, persistence of delay in gastric emptying was observed in people with type 2 diabetes treated with liraglutide for 8 weeks [30] and people with obesity, but without diabetes, treated for 16 weeks [41]. In the latter study the magnitude of the delay in gastric emptying induced by liraglutide was less at 16 than at 5 weeks, probably indicative of some tachyphylaxis [40]. Women with obesity and polycystic ovary syndrome treated with semaglutide subcutaneously (1.0 mg/wk) for 12 weeks also displayed markedly delayed gastric emptying, with 37% of a solid meal retained in the stomach at 4 hours with semaglutide treatment compared to no gastric retention in the placebo group [43]. Further studies, using appropriate methodologies, to characterise the effect of long-term administration of longer-acting GLP-1RAs on gastric emptying (including the reason(s) underlying the inter-individual variability in their effect) are a priority.

GIP and GLP-1 co-agonists and gastric emptying

Molecules targeting more than one peptide hormone receptor have recently been developed for the treatment of type 2 diabetes and obesity. Tirzepatide is the first glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor co-agonist to be approved in Australia for the treatment of type 2 diabetes. It is also approved for the treatment of obesity in the USA. Both the GLP-1R and the GIP receptor (GIPR) are expressed on pancreatic β-cells and activation of these potently stimulates insulin secretion when blood glucose levels are elevated [44]. Unlike GLP-1, gastric emptying is not affected by GIP [45]. Tirzepatide has been studied using the paracetamol absorption test, with evidence that it delays gastric emptying in people with type 2 diabetes [46].

Adverse Effects of GLP-1RAs

Common adverse effects of GLP-1RAs and dual GLP-1 and GIP receptor co-agonists are gastrointestinal, including nausea, vomiting, diarrhoea and constipation. However, the relationship between upper gastrointestinal symptoms and slowing of gastric emptying by GLP-1RAs is weak [25, 38]. Therefore, the presence of gastrointestinal side effects is not a reliable indicator of the degree of slowing of gastric emptying or the presence of gastroparesis. In individuals with type 1 and type 2 diabetes, contrary to expectation, the correlation between symptoms and the rate of gastric emptying is not simply 'cause and effect' i.e. whether emptying is normal, delayed or accelerated cannot be predicted with confidence on the basis of symptoms [47]. That this is also the case with GLP-1RAs is, accordingly, to be expected.

Recently, case reports and small case series of retained gastric contents at the time of gastroscopy or anaesthesia, in people with diabetes and/or obesity treated with GLP-1 RAs, have been published [48-55]. In interpreting these reports it should be appreciated that, even in the absence of GLP-1RA treatment, the retention of gastric contents, despite apparently adequate fasting, is not rare and occurs more frequently in people with diabetes [56]. Nevertheless, the evidence supporting an association between GLP-1RAs and retention of gastric contents is convincing. These reports suggest that GLP-1 RAs pose a threat to periprocedural patients, by increasing the risk of pulmonary aspiration of regurgitated gastric contents. To date, there have been 6 case reports of pulmonary aspiration at the time of endoscopy or anaesthesia in patients treated with GLP-1RAs [50, 51, 54, 55]. A large population-based, retrospective cohort study using a health insurance database (including ~800,000 patients undergoing endoscopy) found a higher incidence rate of aspiration pneumonia (0.83% vs 0.63%) in GLP-1RA users compared to non-users, associated with a significantly higher risk of aspiration pneumonia (hazard ratio 1.33; 95% confidence interval 1.02–1.74; p=0.036). When subgrouped by endoscopy type, the risk appeared to be associated with upper endoscopy, being observed in those who underwent upper endoscopy, combined upper and lower endoscopy but not lower endoscopy alone [57]. Retrospective case-control studies of patients undergoing upper gastrointestinal endoscopy have found a 4- to 10-fold increase in the frequency of residual gastric contents with GLP-1RA use compared with controls [49, 50, 58]. Although only anecdotal, case reports found that retained gastric contents were present despite appropriate fasting, of 8 hours for clear fluids to 20 hours for solids [52]. A small prospective observational study of overnight fasted healthy volunteers, 10 of whom were taking semaglutide for weight management and 10 controls who were not taking semaglutide, found residual intragastric solids on ultrasound in 90% of semaglutide-treated volunteers compared with 20% of control volunteers. Limitations of this study are that the dose of semaglutide varied from 0.25 – 0.75 mg weekly and the majority of volunteers taking semaglutide had been treated for less than 4 weeks [59]. A retrospective study of 1512 individuals taking GLP-1RAs and undergoing oesophagogastroduodenoscopy found retained gastric contents in 9.4%, primarily consisting of solid residue (78.9%) [60].

Although case reports, retrospective observational studies and small prospective studies are usually insufficient to inform clinical practice, the safety concern regarding the periprocedural use of GLP-1 RAs, has recently led a number of overseas bodies to produce clinical practice recommendations regarding the periprocedural use of GLP-1RAs [61-64].

Table 1: GLP-1 RAs and Dual GLP-1 and GIP co-agonists registered for use in Australia

Agent	Receptor agonism	Elimination half-life	Administration schedule	Trade name	Status
Exenatide twice daily	GLP-1	3.3 – 4.0 hours	Twice daily	Byetta	Withdrawn
Liraglutide	GLP-1	12.6 – 14.3 hours	Once daily	Victoza (up to 1.8 mg) Saxenda (up to 3.0 mg)	
Exenatide once weekly	GLP-1	3.3 – 4.0 hours[1]	Once weekly	Bydureon	Withdrawn
Dulaglutide	GLP-1	4.7 – 5.5 days	Once weekly	Trulicity	
Semaglutide	GLP-1	5.7 – 6.7 days	Once weekly	Ozempic (up to 1 mg) Wegovy (up to 2.4 mg)	
Tirzepatide	GLP-1 & GIP	4.2 – 6.1 days	Once weekly	Mounjaro	

[1]Active ingredient encapsulated in microspheres of poly-(d,l-lactide-co-glycolide) to extend half-life

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