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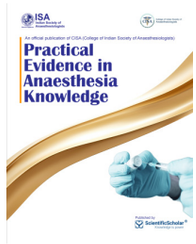

REVIEW ARTICLE

The widespread adoption of glucagon-like peptide-1 receptor agonists in the management of obesity and its implications for the anaesthesiologist and intensivist: A narrative review

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ABSTRACT

Currently, there is a worldwide pandemic of overweight and obesity. The consequences of obesity include non-communicable diseases such as ischaemic heart disease, hypertension, stroke, diabetes mellitus, cancer, and premature death. Obesity is now treated as a disease. Bariatric surgery is the gold standard to treat obesity; however, pharmacological agents are now being widely adopted in the management of obesity. This only means that the number of persons on anti-obesity drugs is on the rise, and they can present for surgery, both bariatric and non-bariatric, and in the intensive care unit. Glucagon-like peptide-1 receptor agonists (GLP-1 RA) are currently the most widely prescribed drugs for diabetes mellitus and obesity, and newer drugs are coming up. The anaesthesiologist and intensivist managing these cases need to be aware of these drugs, their pharmacology, and how they can affect the anaesthetic management and perioperative outcomes. New guidelines for these medications have been released to guide clinical practice for anaesthesiologists. We conducted a literature search related to this topic using databases and search engines (Medical Literature Analysis and Retrieval System Online [MEDLINE], Embase, Scopus, PubMed, and Google Scholar) using words such as 'obesity,' 'GLP1-agonists,' 'semaglutide,' 'tirzepatide,' 'perioperative period,' 'adverse effects.' The search revealed some systematic reviews, meta-analyses, original articles and case reports regarding the safety and efficacy of newer anti-obesity drugs and some interesting perioperative observations and clinical experiences related to their use in the surgical patient. We discuss in this narrative review the current widespread adoption of the new weight loss drugs and its implications in anaesthesia and critical care.

Keywords: GLP1-agonists, obesity, perioperative period, semaglutide, tirzepatide

INTRODUCTION

'Overweight' and 'obesity' are currently the conditions that have affected many countries in the world. Obesity can predispose to the development of serious non-communicable diseases such as ischaemic heart disease, hypertension, stroke, diabetes mellitus (DM), cancer, and premature death. The obese population is now increasingly consulting physicians, nutritionists, and bariatric surgeons for treatment and support. The management of obesity depends on several factors, such as the stage of obesity, the presence of comorbidities, and patient cooperation.

Bariatric surgery is the gold standard to treat obesity; however, pharmacological agents are now being widely adopted in the management of obesity. This only means that the number of persons on anti-obesity drugs is on the rise, and they can present for surgery, both bariatric and non-bariatric. Also, critically ill patients admitted to the intensive care unit (ICU) may have been receiving these medications prior to admission, which can present challenges to the intensivist. Glucagon-like peptide-1 receptor agonists (GLP-1RA) are currently the most widely used drugs in the management of type 2 DM and obesity. Most anaesthesiologists are aware of the health hazards of obesity and how obesity can pose a significant threat to postoperative outcomes and present challenges in the anaesthesia management; however, not many are aware of the current widespread adoption of the new weight loss drugs and their perioperative implications. The purpose of this narrative review is to make the anaesthesiology practitioners and intensivists aware of the rising number of patients on anti-obesity drugs, the pharmacology of these drugs, and how they can affect the anaesthetic and intensive care management and perioperative outcomes. We conducted a literature search (over the last 20 years) related to this topic using databases and search engines (Medical Literature Analysis and Retrieval System Online {MEDLINE}, Embase, Scopus, PubMed, and Google Scholar) from 31st October 2024 to 30th November 2024 using key terms such as 'obesity,' 'GLP1-agonists,' 'semaglutide,' 'tirzepatide,' 'perioperative period,' 'adverse effects.' All six authors were involved in the literature search. The search revealed some systematic reviews, meta-analyses, narrative reviews, original articles, case reports, case series, and editorials regarding the safety, efficacy, and perioperative concerns of newer anti-obesity drugs. Articles that had interesting and relevant information related to the topic were sorted out, and the interesting observations and information thereby collected are presented in this review.

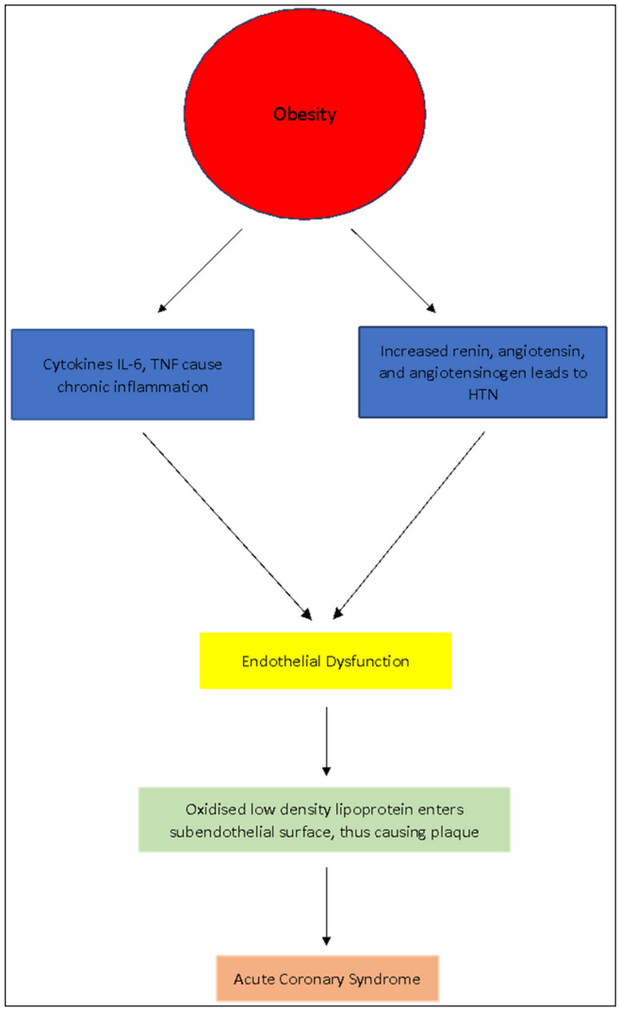

Figure 1: Pathogenesis of chronic inflammation and hypertension secondary to obesity leads to vascular dysfunction. IL-1: Interleukin-1, TNF: Tumour necrosis factor, HTN: Hypertension. Source: Original/ Pahal Sehgal/Naina Jakhar

REVIEW

The obesity pandemic

Charles Darwin, in his theory of evolution, gave the concept of survival of the fittest.[1] As life evolves, only the fittest survive. The fit was defined as one who could adapt to the changing environment. But we have not adapted to change in our milieu. Energy intake is more than energy expenditure and resulted in the obesity pandemic.[2]

Pathophysiology of obesity

The human body is designed to store energy in the form of triglycerides in more than a billion adipocytes.[3–5] This was used to help in survival in periods of drought when there was not enough food supply. However, in modern times, obesity has continued to increase, even in developing countries, due to unhealthy diets, culture, and low physical activity. Obesity has been defined as a body mass index (BMI) of more than 30 kg/m^2. However, for Asians, the cut-off BMI for being obese is 27.5.[6,7]

Adipocytes keep on accumulating triacylglycerols until they become turgid and burst. Following this, there is a breakdown of triglycerides, and free fatty acids (FFA) are spilled into the circulation, triggering inflammation and the release of cytokines [Figure 1], mainly interleukin-1 (IL-1) and tumour necrosis factor (TNF) alpha.[8] The FFA and cytokines cause widespread low-grade chronic inflammation.[9,10] This dephosphorylates insulin receptors and causes insulin resistance, which leads to hyperglycaemia and dyslipidaemia. Furthermore, the renin, angiotensin, and angiotensinogen secreted by adipocytes add to the

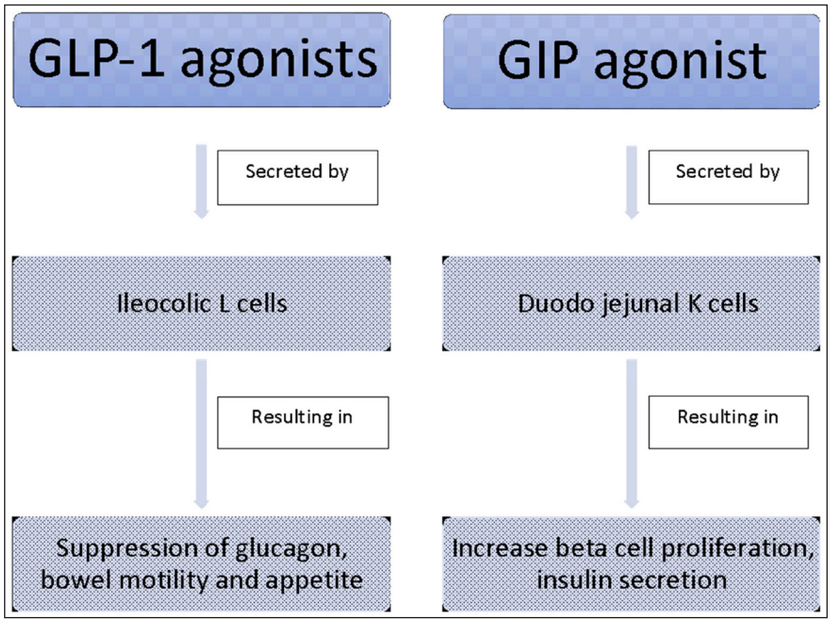

Figure 2: The twincretin effect: Glucagon-like peptide-1 (GLP-1) secreted from L cells from the ileocolic area causes suppression of glucagon and bowel motility. A glucose-dependent insulinotropic polypeptide (GIP) secreted from K cells of the duodenal jejunal area causes increased insulin secretion and beta cell mass. Source: Original/Pahal Sehgal/Naina Jakhar

normal physiological renin-angiotensin system.[11–15] The result of this process is hypertension and endothelial dysfunction. This primes the conditions for oxidised low-density lipid (LDL) to make its way to the sub-endothelial area. Macrophages engulf the oxidised LDL particles to form foam cells. T lymphocytes follow macrophages, and an atheromatous plaque is formed, which is waiting to rupture and produce an acute coronary event.

Moreover, adipocytes secrete an increased amount of plasminogen activator inhibitor-1, which leads to a prothrombotic state. An insulin-resistant, metabolically unhealthy, and immune dysfunctional state is thus created.

Pharmacological interventions for obesity

Diet and exercise have always been the first line of recommendation for tackling obesity. But that is easier said than done. The medical world has been rather slow with regard to the development of effective pharmacotherapy for obesity. Before the advent of GLP-1RA, the effective weight loss from pharmacotherapy was anywhere between 3% and 8.6%.[3] Also, the safety profile of most of the anti-obesity drugs remained questionable, and many of them were withdrawn from the market.

With the introduction of GLP-1RA, there have been rapid strides in the arena of weight loss drugs. The American Diabetes Association (ADA) in their latest guidelines in 2023 has laid great emphasis on GLP-1RA along with sodium-glucose cotransporter-2 (SGLT-2) inhibitors in the management of Type 2 DM, and weight loss has been stressed upon.[16]

Currently, GLP1-agonists are widely and increasingly being prescribed by physicians, endocrinologists, and bariatric surgeons for the management of Type 2 DM and obesity. They are prescribed as add-ons to diet and exercise. Obese patients with BMI >35 kg/m^2 and comorbidities are often put on these drugs to achieve a weight loss of 5%–10% to get them into the fitness bracket for surgery.

Among the GLP-1 agonists, semaglutide has been found to be the most effective to date for weight loss. Tirzepatide has gone a step further, as unlike semaglutide, it is a twincretin with both GLP-1 agonist and glucose-dependent insulinotropic polypeptide (GIP) action. Under physiological conditions, GLP-1 is secreted in response to oral nutrient intake from ileocolonic L cells concomitantly with GIP from duodenojejunal K cells. GIP is the main incretin hormone and is responsible for most of the incretin effect [Figure 2]. However, its effect is blunted in people with Type 2 DM, indicating GIP resistance. However, the resistance may be reversed by improving glycaemic control. Together, these two incretins lead to beta cell proliferation and increased insulin secretion in a glucose-dependent manner.

The receptors for GLP-1 are more ubiquitous, and the drugs have more widespread actions. They decrease glucagon production and suppress appetite by direct action on appetite centres. They also have a profound effect on bowel motility, as there is widespread distribution of GLP-1 receptors in the myenteric plexus of the bowels. In the physiological state, the effect of these incretins is very short-acting, as they are degraded by dipeptidyl peptidase IV. This is where synthetic incretins come into play. Their half-life is prolonged by an increase in their binding to albumin with the help of fatty acids.

The GLP1-agonists and GIP agonists are administered by different routes, and their frequency of administration is variable [Table 1].[17-19] Initially, small doses of the drug are started. The dose is gradually increased to a maximum dose which the patient can tolerate without suffering from the side effects.

Table 1: GLP-1 and GIP RA Medications

Generic drug	Medication class	Indication	Half-life, Duration of action	Administration Route Frequency Dose	Brand name (as per indication)	
					For diabetes mellitus	For weight loss
Exenatide	GLP-1 RA	Diabetes mellitus	3.3–4 h Short-acting	Subcutaneous Twice daily 5–10 µg	Byetta*	-
Exenatide	GLP-1 RA	Diabetes mellitus	3.3–4 h Short-acting	Subcutaneous Once weekly 2 mg weekly	Bydureon*	-
Lixisenatide	GLP-1 RA	Diabetes mellitus	2.6 h Short-acting	Subcutaneous Once daily 5 µg	Lyxumia*	-
Liraglutide	GLP-1 RA	Diabetes mellitus, obesity	12.6–14.3 h Long-acting	Subcutaneous Once daily 1.8 µg	Victoza	Saxenda
Dulaglutide	GLP-1 RA	Diabetes mellitus	4.7–5.5 d Long-acting	Subcutaneous Once weekly 1.5 mg	Trulicity**	-
Semaglutide	GLP-1 RA	Diabetes mellitus	5.7–6.7 d Long-acting	Subcutaneous Once weekly 0.5–1 mg	Ozempic	Wegovy***
Semaglutide	GLP-1 RA	Diabetes mellitus, obesity	5.7–6.7 d Long-acting	Oral once daily	Rybelsus	-
Tirzepatide	Dual GLP-1/GIP RA	Diabetes mellitus, obesity	5 d Long-acting	Subcutaneous Once weekly	Mounjaro	Zepbound***

*: Drug discontinued (product withdrawn), **: Limited availability due to global supply pressures, ***: Becoming increasingly popular for weight loss, d: Days, GIP: Glucose-dependent insulinotropic polypeptide, GLP: Glucagon-like peptide, h: Hours, RA: Receptor agonists

The safety and efficacy profile of tirzepatide and semaglutide

Long-term cardiovascular outcome trials with GLP-1RA have confirmed that GLP-1RA are safe and do not increase the long-term risk of major adverse cardiovascular events (MACE).[20] Several studies actually showed a reduction in the risk of MACE with GLP-1RA compared with standard treatment.

The side effects of these drugs are largely related to the gastrointestinal tract and include nausea, dyspepsia, vomiting, diarrhoea, abdominal pain, and constipation.[19] Of these, nausea, vomiting and diarrhoea are the most common.[21] Neurological side effects include headaches and dizziness. Cardiovascular side effects include mildly increased heart rates. Infections such as nasopharyngitis, influenza, and urinary tract infections have also been reported. Liraglutide and semaglutide show a stronger potential association with pancreatitis than the other GLP-1RA [Table 2].[19,21,22]

The safety profile of tirzepatide and its effectiveness have been well illustrated in the randomised controlled SURMOUNT-1 trial, in which more than 2,500 people were followed for 72 weeks and assessed for weight loss.[23] Most of the people had a BMI of >30 kg/m^2 but people with a BMI of 27–30 kg/m^2 with at least one obesity-related complication were also included. Three groups with doses of 5, 10 and 15 mg were followed along with placebo. The primary endpoint was a

Table 2: Adverse Effects of GLP-1 RAs

Generic drug	Adverse effects
Exenatide	Nausea
Lixisenatide	Hypoglycaemia, Nausea, Vomiting, Headache, Dizziness
Liraglutide	Nausea, Vomiting, Diarrhoea, Constipation, Abdominal Pain, Pancreatitis, Kidney Injury
Victoza	Hypoglycaemia, Gastroenteritis, Increased Pulse Rate
Saxenda	Nausea, Diarrhoea, Abdominal Pain, Constipation
Dulaglutide	Nausea, Vomiting, Diarrhoea, Hypoglycaemia, Acute Pancreatitis(rare)
Semaglutide	Nausea, Vomiting, Diarrhoea, Constipation, Abdominal Pain, Pancreatitis, Kidney Injury, Diabetic Retinopathy, Thyroid C-Cell Tumours
Ozempic, Wegony	Nausea, Diarrhoea, Constipation
Rybelsus	Nausea, Diarrhoea
Tirzepatide	Abdominal pain, nausea, vomiting, bloating, dyspepsia, constipation, diarrhoea, sinus tachycardia, acute kidney damage, thyroid C-cell tumours, acute pancreatitis, especially if dehydration

GLP-1RAs: Glucagon-like peptide-1 receptor agonists

weight loss of more than 5% from baseline. Significant weight loss was observed at the end of 72 weeks, with more than a 90% completion rate. Also, 15%–36% of people had weight loss >25%. The response was incremental, with an increase in the dose of tirzepatide. The lipid profile also improved with an increase in high-density lipids (HDL) and a decrease in non-HDL cholesterol and triglycerides. The most common side effect was nausea, and it was the most common cause for discontinuation of the medication.

Similar results were seen in the SURPASS-2 clinical trial when three doses of tirzepatide 5, 10, and 15 mg were compared to semaglutide 1 mg.[24,25] Semaglutide 2 mg was not used as that was not available at that time. It was an open-label study, as syringes for tirzepatide and semaglutide are different. Unlike the SURMOUNT-1 trial, the patients were followed for only 40 weeks with a significant reduction in glycosylated haemoglobin (A1C) so that an A1C drop of more than 2% was seen with all three doses of tirzepatide as compared to semaglutide, which showed a drop of 1.86%. The weight loss was 8.5% from baseline for all three doses of tirzepatide, with incremental weight loss with higher doses. The weight loss with semaglutide was 6.7%. The results for semaglutide were consistent with previous SUSTAIN trials with semaglutide.[26] The most common side effect was nausea, and it was the most common cause of dropping out of the trial. There were 13 deaths in the study. Five deaths were attributed to coronavirus disease (COVID)-19, and four others were related to cardiovascular causes. The cause of two deaths could not be determined. It must be noted that the trial was conducted during the peak of the COVID-19 pandemic but still had a high completion rate. Also, there were two cases of pancreatitis in each of the 10 and 15 mg groups of tirzepatide and three patients in the semaglutide group. The actual relation of these drugs to pancreatitis remains obscure, though these drugs come with a product insert, which puts pancreatitis as a contraindication for their use. Also, there is a black box warning for the use of these drugs in patients with a family and personal history of medullary thyroid cancer.

Semaglutide had shown a significant reduction in MACE in the SUSTAIN cardiovascular outcome trial (CVOT).[27] This study had more than 3,000 participants who were given either semaglutide or placebo. The semaglutide group with doses of 0.5 or 1 mg weekly showed a significant reduction in non-fatal myocardial infarction and non-fatal stroke. The rate of new or worsening nephropathy was also lower in the semaglutide group. Recently, a randomised controlled trial of semaglutide (FLOW) to assess its effect on chronic kidney disease (CKD) was stopped before its completion as it showed a significant effect in slowing the progress of CKD. The FLOW trial (NCT03819153) had more than 3,000 participants and was stopped before its completion as it met its pre-determined end.

The ongoing trial, SURPASS-CVOT, is expected to provide definitive evidence on the cardiovascular safety and efficacy of tirzepatide as compared with dulaglutide, which has established cardiovascular benefits.[28–30]

Other upcoming drugs and formulations for weight loss

Other drugs that figure prominently in the ADA 2023 guidelines for glycaemic control are SGLT-2 inhibitors. These have added benefits in the treatment of heart failure and in slowing the progression of CKD. They do cause glucosuria and thereby energy expenditure leading to weight loss in patients with Type 2 DM. However, when used as a single therapeutic agent, the weight loss is not significant as there is compensatory hyperphagia. When used in combination with GLP-1 agonists, these drugs serve as good weight-loss medications in patients with Type 2 DM.[31,32]

Retatrutide is a new drug which is a triple agonist acting on glucagon receptors in addition to GLP-1 and GIP receptors. It is in the phase II trial, and the results of this were recently published in the New England Journal of Medicine. It produced significant weight loss and is bound to be the most successful weight loss medication.[33] It led to a 24.2% weight loss in patients on the highest dose at just 48 weeks. This is better than the weight loss results seen in the SURMOUNT

Table 3: Guidelines and Recommendations for the Perioperative Management of Patients on GLP-1 Agonists
For patients on a daily dose of GLP-1 agonists, the drug should be held on the day of the surgery.[22]
For those on weekly doses of GLP-1 agonist, the drug needs to be stopped a week before the surgery, e.g. dulaglutide, semaglutide, and tirzepatide.[22]
If GLP-1 agonist is withheld preoperatively for a longer duration, a clinical endocrinologist needs to be consulted so that glycaemic control can be optimised.[22]
On the day of the elective procedure, if the patient has gastrointestinal symptoms such as severe nausea/vomiting/retching, abdominal bloating, or abdominal pain, one can consider delaying the procedure and discussing the concerns of the potential risk of regurgitation and pulmonary aspiration of gastric contents with the proceduralist/surgeon and the patient.[22]
On the day of the elective procedure, if the patient has no gastrointestinal symptoms and the GLP-1 agonists have been held as advised, one can proceed as usual.[22]
On the day of the elective procedure, if the patient has no gastrointestinal symptoms but the GLP-1 agonists were not held as advised, one has to proceed with 'full stomach' precautions or consider evaluating gastric volume by ultrasound, if possible, and if proficient with the technique. If the stomach is empty, one can proceed as usual. If the stomach is full or if gastric ultrasound is inconclusive or not possible, the procedure can be delayed, or the patient can be treated as a 'full stomach' and managed accordingly.[22]
In those taking GLP-1 agonists within 4 weeks prior to elective upper endoscopy, a fluid diet should be followed for 24 hours before endoscopy.[49]
In case of an emergency endoscopic procedure to be done in a patient on GLP-1 agonist, a single dose of intravenous erythromycin 3 mg/kg can accelerate gastric emptying within 15 minutes.[49]
Anaesthetists should undertake individualised clinical assessment and precautions, which include regional anaesthesia, tracheal intubation, modified rapid sequence intubation; ramped position, awake tracheal extubation, avoidance of first-generation supraglottic airway devices and pre-operative gastric ultrasound.[48]
Use of GLP-1 RAs in the perioperative period should be based on shared decision-making of the patient with procedural, anaesthesia, and prescribing care teams balancing the metabolic need for the GLP-1 RA with individual patient risk. This can be achieved by developing multidisciplinary protocols/procedures appropriate for individual practices.[47]
The escalation phase of GLP-1 agonist, a higher dose of GLP-1 agonist, weekly dosing, the presence of GI symptoms, and other medical conditions can elevate the risk of delayed gastric emptying.[47]
When an elevated risk of delayed gastric emptying and aspiration exists the withholding of GLP-1 RAs should be balanced with the surgical and medical risk of inducing the potential for a hazardous, metabolic disease state, like hyperglycaemia. [47]
The safe use of GLP-1 RAs in the perioperative period should include efforts to minimise the aspiration risk of delayed gastric emptying. These include preoperative diet modification, rapid sequence induction of general anaesthesia for tracheal intubation, and point-of-care gastric ultrasound to assess aspiration risk.[47]

GLP: Glucagon-like peptide, GLP-1 RA: Glucagon-like peptide 1 receptor agonist, GI: Gastrointestinal

trial with tirzepatide, wherein the patients were followed up for 72 weeks.

As GLP-1RA are peptides, their oral bioavailability is very poor. Semaglutide is the only GLP-1 agonist which is available as an oral formulation. Orforglipron is the first non-peptide GLP-1RA used orally once a day and is associated with significant weight loss. In a double-blind, randomised controlled trial, 272 people were randomised to receive orforglipron in doses of 12, 24, 36 and 45 mg versus placebo. At 36 weeks, weight loss was seen from 9.4% to 14.7%, depending on the dose used.[34]

Perioperative implications of GLP-1 agonists

GLP-1 agonists present plenty of potential positive perioperative effects. As these medications have been shown to be effective adjuncts in the treatment of Type 2 DM, cessation of these drugs in the perioperative period may disturb blood glucose control.[35] However, their continuation may enhance the risk of gastric aspiration because of their effects of decreasing gastric motility.

History of intake of GLP1-RA should be asked in obese patients during the preoperative assessment. If there is a history of intake, the medication group, dose, indication, route of administration, frequency, and encountered side effects should be noted. Clear instructions on the stoppage or continuation of these drugs before the scheduled surgery need to be given. History of opioid use and presence of comorbidities such as Type 2 DM must be elicited because these can prolong gastric emptying and worsen the risk of aspiration with GLP-1 agonist use. Gastric ultrasonography on the table before induction may be useful to evaluate the

gastric contents.[35] Rapid sequence intubation should be done when the concern persists for the risk of perioperative aspiration.

Benefits of continuing GLP-1RA during the perioperative period

Perioperative studies of long-acting GLP-1RA showed better glycaemic control compared with placebo or standard care with insulin in the perioperative period without a higher risk for developing hypoglycaemia.[18]

Studies in cardiac surgery show glycaemia benefit of GLP-1RA (liraglutide and exenatide) when compared to insulin and delayed initiation and lower doses of insulin needed for glycaemic control.[17]

Studies in non-cardiac surgery show benefits such as better glycaemic control and fewer prosthetic joint infections. These effects are attributed to the immunomodulatory and anti-inflammatory effects of GLP-1RA.[17]

Nevertheless, there is a lack of data on the benefits of continuing GLP-1RA in patients with obesity.

Risks of continuing GLP-1RA during the perioperative period

GLP-1 agonists are known to enhance gastroparesis, and there are legitimate concerns for aspiration during the induction of general anaesthesia.[36–42] Symptoms of nausea and vomiting suggest delayed gastric emptying, but data show that even when patients report no symptoms, they can still have significantly altered gastric emptying times. There are a number of case reports describing episodes of perioperative pulmonary aspiration due to delayed gastric emptying in patients taking GLP-1RA. However, long-standing diabetes was often present in the reported cases, and it is not sure whether the GLP-1RA was the direct cause of pulmonary aspiration.[42]

In most of the case reports and case series that have reported aspiration in patients taking GLP-1RA, the patients had followed current recommendations for fasting (i.e., 8 hours fasting time for solids and 2 hours for liquids). The length of fasting has not been reported in a few case reports. Also, the majority of aspiration events occurred in patients receiving monitored anaesthesia care.[17] In the studies on gastric emptying in patients on GLP-1RA using ultrasonography/computed tomography/nuclear scintigraphy/acetaminophen absorption test, there was evidence of prolonged gastric emptying time for solids. The gastric emptying effects are more pronounced in the first few weeks after initiating GLP-1RA or with escalating doses. There is a difference between short- and long-acting drugs and their effects on gastric emptying. Clinical studies have identified a higher proportion of retained gastric content in patients taking semaglutide.[35] The plasma concentration of short-acting drugs peaks and decreases rapidly. Gastric emptying may be impacted by intermittent stimulation of the GLP-1 receptor more than that by long-acting drugs, which continuously stimulate the receptors, resulting in tachyphylaxis. Patients on short-acting medications may develop tachyphylaxis after weeks to months compared to 4–5 weeks for long-acting preparations. However, there are many limitations regarding these studies, e.g. these studies have not assessed effects beyond 4–6 hours. Also, the data are heterogeneous in non-procedural and non-surgical settings,[17] and it may not be easy to extrapolate their findings to the perioperative setting.

In a recently published meta-analysis, the risks and benefits of using GLP-1RA were compared with control in surgical and nonsurgical procedures under anaesthesia or sedation. It was concluded that compared to control, pre-procedural GLP-1RA increased the rate of gastrointestinal symptoms and the risk of elevated residual gastric content in spite of adhering to fasting guidelines. GLP-1RA improved glycaemic control and decreased the rate of rescue insulin administration. There was no significant difference in the rates of perioperative hypoglycaemia or hyperglycaemia, postoperative inotropic support, postoperative nausea and vomiting, atrial fibrillation, and 30-day mortality.[43]

GLP-1RA have also been reported to have been used for the management of Type 2 DM and obesity in children in the age group of 10–18 years. Their anaesthetic implications are the same as in adults.[22]

Guidelines and recommendations for the preoperative cessation of GLP-1RA

There are guidelines and endorsed statements from different societies that provide varying recommendations regarding the perioperative management of these drugs.[44–49] The American Society of Anesthesiologists has come out with consensus-based guidelines for the management of GLP-1RA in the perioperative settings [Table 3].[22,47–49] There is no evidence to suggest the optimal duration of fasting for patients on GLP-1 agonists. Adequate evidence is yet to be gathered.[22,50] Nevertheless, a recent review concludes that there is insufficient evidence to frame recommendations regarding the ideal time when GLP-1RA should be stopped before elective surgery, and an individualised, evidence-based approach needs to be adopted.[50] In patients with Type 2 DM, there is concern that prolonged cessation before surgery will have a detrimental effect on perioperative glycaemic control, and discussion with an endocrinologist is advised. The intake of these drugs should be stopped for a period of at least three drug half-lives prior to an elective surgical procedure in patients taking GLP1-RA for weight management.[51] In some specific situations, stopping GLP-1RA in patients already taking these should be considered,

e.g., in patients undergoing pancreatic surgery or with postoperative pancreatitis, in those with acute kidney injury requiring renal replacement therapy, and in cases of postoperative ileus.[18] Many of the patients on GLP-1RA might also be on SGLT-2 inhibitors. SGLT-2 inhibitors cause postoperative euglycaemic ketoacidosis if not stopped preoperatively. Hence, they have to be stopped at least 72 hours before surgery.[52]

Implications of GLP-1RA in critical care

The action of GLP-1 agonists can have significant implications for the management of critically ill patients in terms of gastric emptying, tolerance of enteral nutrition, and glycaemic control.[53] GLP-1RA have been reported to attenuate stress-induced hyperglycaemia, with a reduced risk of hypoglycaemia when compared to insulin administration.[54,55] GLP-1 is said to exert neuroprotective, cardioprotective, nephroprotective, and immunomodulatory effects by acting through GLP-1 receptors located on many vital organs. Critically ill ICU patients may be unable to secrete sufficient amounts of GLP-1. GLP-1 agonists may be useful in critically ill patients in this regard.[56] A systematic review of randomised controlled trials found that GLP-1RA treatment in surgical and critically ill patients reduces blood glucose levels and insulin administration without increasing hypoglycaemia episodes compared with control groups.[57] The risk of delayed gastric emptying and pulmonary aspiration exists in critically ill patients on GLP-1RA, especially those who are comatose and those on non-invasive ventilation. The effects of GLP-1RA, such as semaglutide, with prolonged half-lives can remain through the patient's stay in the ICU even if the drug gets discontinued on admission to the ICU.[53] The intensivist who is managing these patients has to keep this in mind.

The future of GLP-1RAs and their perioperative implications

The use of GLP-1 agonists is likely to expand beyond Type 2 DM and obesity.[58] Their use in the treatment of metabolic liver disease, peripheral arterial disease, Parkinson's disease, Alzheimer's disease and polycystic ovarian disease is being explored.[58,59] They have already shown cardiovascular and cardio-renal benefits. The challenge remains to make these drugs affordable worldwide. Liraglutide has gone off-patent in 2024 and will likely become more affordable as we move forward. Currently, semaglutide and tirzepatide are not available in India officially. There are reports of these being bought in the black market. This, again, is a safety issue. Also, when available, the cost is likely to be high. However, once these issues are solved, the prescription and consumption of these drugs will increase, and so will the chances of the anaesthesiologist/intensivist encountering a patient on GLP-1 agonists. Gastric ultrasonography can help the practitioner manage such a case.[59] That means the acquisition of technical expertise in gastric ultrasound is necessary for anaesthesiologists and intensivists. Robust research on several perioperative and critical care aspects of these drugs that are still poorly understood, especially the ideal time to stop the drug before surgery, postoperative outcomes, and the impact of long-acting GLP-1RA on glycaemic control in critically ill patients, is needed. Clinicians and practitioners need to report and publish their perioperative observations and experiences in patients on GLP-1 agonists. All this will help to develop an evidence-based perioperative assessment and management plan for patients taking GLP-1RA.

CONCLUSION

Newer drugs are being widely adopted in the management of DM and weight loss. The possibility of an anaesthesiologist/intensivist encountering a patient on anti-obesity drugs such as GLP1-RA is increasing by the day. These drugs have several perioperative implications, both positive, such as improvement in cardiovascular profile, and negative, such as a potentially higher risk of aspiration. This can be managed by having a thorough knowledge of the pharmacology of these drugs and by adopting a cautious approach in the perioperative setting. There are several knowledge gaps regarding the use of these drugs in the perioperative and critical care setting. These must be addressed and further researched, and high-quality evidence has to be built upon their clinical application.

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