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GLP-1 agonists in anaesthetic practice - a review of clinical data and recommendations

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Abstract

Introduction: Glucagon-like peptide-1 receptor agonists (GLP-1 RA) are a group of drugs originally used for the treatment of type 2 diabetes and now also for obesity and off-label indications. With the increasing popularity of the use of these substances, the likelihood of encountering such a patient in the operating theatre is increasing, creating new challenges for anaesthetic practice.

Purpose: The aim of the following paper is to review current clinical data on patients using GLP-1 agonists in perioperative care and to provide recommendations from scientific societies for the management of these patients.

Materials and research methods: The article is based on an analysis of research available on PubMed and Google Scholar. A literature review was conducted using the following keywords and medical subject headings: glucagon-like peptide-1 agonists; GLP-1 RA; perioperative period; gastric emptying; preoperative management; aspiration. The analysis included clinical trials, systematic reviews and expert consensus statements.

Results: GLP-1 analogues show a number of beneficial metabolic, cardioprotective and nephroprotective effects, which may improve the overall health of patients. At the same time, these drugs, by delaying gastric emptying, increase the risk of regurgitation and pulmonary aspiration during induction of anaesthesia.

Conclusion: Despite the growing population of patients using GLP-1 agonists, there are still no detailed reports on the basis of which guidelines for ideal management can be developed. Therefore, despite the existence of general recommendations from societies, special caution and an individual approach when working with such patients is advisable.

Keywords: glucagon-like peptide-1 agonists; gastric emptying; aspiration; anaesthesia; perioperative management

Introduction

In recent years, the medical world has seen a significant increase in the use of GLP-1 receptor agonists (glucagon-like peptide-1 receptor agonists, GLP-1 RA), which have revolutionized approaches in the treatment of type 2 diabetes as well as in the treatment of obesity. This group of drugs is particularly clinically attractive in the treatment of people at high risk of cardiovascular disease and chronic kidney disease. Representatives of this class are characterized by effective lowering of fasting plasma glucose and glycated hemoglobin levels. Importantly, glycemic control is characterized by a low risk of hypoglycemia, with no discernible differences in effect between representatives of GLP-1 analogues. Their mechanism of action is based on mimeticism of the natural incretin hormone GLP-1, which stimulates insulin secretion in a glucose-dependent manner. Weight loss in users of this class of drugs results from delayed gastric emptying and increased subjective feelings of satiety. [1]

Due to their therapeutic efficacy, more and more patients are taking these drugs not only for diabetes, but also for the treatment of obesity, metabolic syndrome and off-label applications e.g. Alzheimer's disease, Parkinson's disease. [2,3] Epidemiological and market data show that the rapid, rapid, increase in the use of GLP-1 agonists is becoming a sustainable trend. Watanabe et al. using data from the University of California Health Data Warehouse described an increase in the number of GLP-1 users between 2014 and 2022.

Using Ozempic (semaglutide) as an example, the upward trend was from 569 in 2019 to 7667 in 2020. [4] Mahase E. reports up to a 700% increase in the use of GLP-1 analogues in the US study population over the period 2019-2023. [5] This phenomenon significantly increases the likelihood of working with such patients in the operating theatre.

This raises significant challenges from the perspective of anaesthesia specialists regarding the pharmacological profile of this group of drugs. One of the key clinical concerns is the effect of these drugs on gastrointestinal motility - delaying gastric emptying. Patients using GLP-1 RA may be at increased risk of regurgitation and aspiration of gastric contents during induction of general anaesthesia, even despite adherence to standard preoperative starvation recommendations. [6] Additionally, there are concerns about interactions with premedication drugs, altered oral absorption. Despite this, there is still a lack of consistent information from randomised clinical trials on which medical staff can fully base their knowledge. In response to these concerns, leading anaesthesia societies, such as the American Society of Anesthesiologists (ASA), have recently published guidelines for the management of patients using GLP-1 analogues in the preoperative period, emphasizing the need to individualise the approach and consider modifications to standard protocols.

The aim of the following review paper is to comprehensively present the latest data on the use of GLP-1 agonists in the context of anaesthesiology. The paper is intended to focus on pharmacokinetic aspects, clinical risks, diagnostic options (e.g. gastric ultrasonography), recommendations from scientific societies and proposed management strategies to minimize the risk of complications and maximize patient safety.

GLP-1 agonists - group characteristics

Glucagon-like peptide-1 receptor agonists are a highly effective group of incretin drugs. Their therapeutic action is based on the activation of GLP-1 receptors located predominantly on pancreatic islet β cells. [7] These receptors are G-protein coupled and their stimulation initiates a number of signaling pathways. The result is increased insulin secretion, decreased glucagon release and ultimately glycemic regulation and appetite control. [8]

They are also present in large numbers in cells of the gastrointestinal tract, heart, vascular smooth muscle, lung, kidney and vagus nerve. [9] The pharmacokinetics of representatives of GLP-1 analogues vary significantly depending on their molecular structure and the pharmaceutical modifications they have undergone. Short-acting preparations, which include exenatide, lyxisenatide, are characterized by a half-life of 2 to 4 hours. This time determines the need for their administration, at least once daily. Long-acting substances are modified accordingly to prolong their elimination time. For example, exenatide, which has an increased duration of action, is placed in microspheres that ensure gradual release from subcutaneous tissue. [10] Dulaglutide is removed longer from the body due to its association with the crystallizing fragment of immunoglobulin G. The long duration of action of albiglutide and semaglutide is in turn due to conjugation with albumin. [11,12] These processes result in long-acting GLP-1 analogues being administered predominantly once a week. [13]

An important aspect of the mechanism of action of GLP-1 analogues is the enhancement of insulin secretion in a manner dependent on the increase in plasma glucose concentration, which explains the low likelihood of hypoglycaemia with therapy with drugs of this group. [14] In addition, these substances can induce β cell proliferation and inhibit cell apoptosis, with beneficial effects on pancreatic health. [9] Glucagon-like receptor-1 activation has an inhibitory effect on glucagon secretion, slows gastric emptying and affects the satiety centre in the hypothalamus, resulting in a therapeutic effect on weight loss. [15] There are reports that also confirm the positive effects of this group of drugs on the cardiovascular system. By reducing inflammation, they have a cardioprotective effect, in addition to lowering systolic blood pressure and increasing fatty acid metabolism. [15,16,17] Consequently, this leads to a reduced risk of cardiovascular incidents, which, in addition to glycaemic control, is a desirable therapeutic effect. [17]

Mechanism of delayed gastric emptying

GLP-1 receptor agonists show significant effects on gastrointestinal motility, which is a desirable effect in diabetes therapy [18]. Delayed gastric emptying accounts for most of the glucose-lowering mechanisms relative to the action on pancreatic islet cells themselves. [12] This leads to a prolonged feeling of satiety after a meal, resulting in reduced energy intake. A long-term caloric deficit induced by a change in eating behaviour initiates significant weight loss. [19]

This effect is due to the complex action of these drugs at the peripheral and central levels. In addition to their regulating effect on gastric peristalsis, GLP-1 analogues also increase pyloric sphincter tone and inhibit duodenal peristalsis. [20,21] The central nature of the action of these drugs is based on the stimulation of GLP-1 receptors in the brainstem and hypothalamic centres [22] and the reduction of gastric motility via the vagus nerve. [23] It has been proven that this effect does not occur in patients after vagotomy. [24]

Evidence of this relationship has been demonstrated by endoscopy [25,26,27], sonography [28,29], scintigraphy [30,31], and after ingestion of radio-labelled carbon [32,33], paracetamol, among others. [34,35,36] A study by Silveira et al. found that the use of semaglutide and the presence of gastrointestinal symptoms in patients in the preoperative period were associated with a significantly increased risk of gastrointestinal content retention. [26] Kobori et al. also showed significantly more frequently observed gastric residual food. [37] Recent data confirm the association of an increased risk of perioperative food content retention with both short-term and long-term use of GLP-1 analogues. [38] It is also worth noting that the delayed gastric emptying effect of these drugs may undergo tachyphylaxis, i.e. a reduction in the intensity of action with long-term use. [39]

In conclusion, delayed gastric emptying is an important effect of glucagon-like peptide-1 receptor analogues, with both beneficial therapeutic aspects in glycaemic control and potential clinical implications, particularly in the context of perioperative care.

Adverse effects to be considered in pre-operative care

The complex effects of GLP-1 analogues on the gastrointestinal tract are also associated with the occurrence of nausea, vomiting and diarrhoea. These are the most commonly reported adverse effects of therapy with these drugs. Their severity depends on the dose of the substance and the duration of action - they are more frequent with short-acting analogues compared with long-acting analogues. There are reports of the effectiveness of slow drug titration to reduce these adverse effects. [40]

Rare adverse effects include acute pancreatitis. Consequently, caution is advised when treating patients with GLP-1 analogues who have a history of an incident of this disease. [41]

The documented effect on slowing gastric motility has led to concerns about the possible impact on altering the absorption of oral drugs. This has also become a focus of interest in the perspective of drugs used in the premedication of surgical procedures. However, to date, no significant effect of any of the GLP-1 analogues tested has been observed. Nevertheless, caution in the use of this group of substances is still recommended. [42]

Consequences for anaesthesiologists

The growing popularity of therapy with GLP-1 analogues calls for a reflection on the implications of their use in anaesthetic practice. The most extensively studied issue to date is that of delayed gastric emptying, the retention of food content, which increases the risk of pulmonary aspiration during anaesthesia. There are reports presenting clinically important evidence of delayed gastric emptying in patients starved long enough, undergoing general anaesthesia and sedation for elective surgery. [43,44,45] The phenomenon of pulmonary aspiration has also been described in preparation for endoscopy. [46,47] The available descriptions of these events involved patients who were taking GLP-1 analogues and fasted for longer than the currently recommended guidelines stated.

The patient described in the study by Klein et al. was starved for 18 hours prior to the procedure prior to elective upper esophageal endoscopy. Despite this, regurgitation and pulmonary aspiration occurred. [46] On the other hand, a woman in the Gulak and Murphy publication became sick despite fasting for 20 hours (solid foods), for 8 hours (clear liquids). [45] A further example is the episode of choking documented by Weber et al. in a patient undergoing hysteroscopy and removal of an endometrial polyp. The rule of adequate fasting in this woman was observed. [43]

The duration of taking GLP-1 analogues in the above cases varied. They were 8 weeks [46], 5 months [45], time unspecified, respectively. [43] In these trials, all participants were obese and had taken the drug within the last week. However, the size and quality of these trials do not allow definitive conclusions to be drawn. A number of studies in the preoperative setting are still needed for clear confirmation. [48]

A number of factors also influence the relationship between taking GLP-1 analogues and delayed gastric emptying despite long fasting times. It is important to remember that the pharmacokinetic and pharmacodynamic profile of the drugs plays an important role. [49] Therefore, the half-life of the substance and the specificity of the product must be taken into account. Studies report that the time from discontinuation of GLP-1 analogues to surgery may be important. The longer the period of time from discontinuation of these drugs, the lower the risk of gastrointestinal content retention. There are reports that discontinuation of a GLP-1 analogue even 7 days prior to planned surgery is associated with a high risk of food debris backlogging. [29] Recent information reports that up to three weeks abstinence from the drug was associated with increased gastric volume and presence of gastric contents. [50] Due to limited evidence, this issue requires more in-depth research.

Perioperative recommendations

Given that there are still few high-quality perioperative studies on which to base recommendations for optimal management, there is a great deal of uncertainty in the care of patients taking GLP-1 analogues. Perioperative management in such a case is discussed by societies and bodies to highlight the seriousness of the problem, which is the potential aspiration of gastric contents into the lungs.

The American Society of Anesthesiologists has updated its guidelines in response to the increasing number of patients treated with GLP-1 analogues. The recommendations suggest discontinuing GLP-1 agonists at least seven days before a planned procedure requiring sedation, general anaesthesia in patients dosed weekly. Short-acting substances taken daily should be discontinued on the day of surgery. [51] From a pharmacological point of view, to maximally minimise the risk of gastric contents stasis and the associated risk of pulmonary aspiration, it would be advisable to discontinue the drug at least 5 of its half-life before the planned procedure. For some drugs of this group, this may be a period of 2 or more weeks. [52] However, these reports raise considerable practical concerns. Such a long period of abstinence from therapy would require special surgical and anaesthetic supervision in the preoperative setting. [53]

If the drug is taken to treat obesity, the abstinence period should be extended to two weeks (three half-lives). In addition, there is a suggestion to combine the discontinuation of the drug with an assessment of patients for symptoms that suggest a risk of delayed gastric emptying - nausea, vomiting, flatulence, abdominal pain. If these symptoms are present, it is advisable to discuss the risk with the patient, consult with the surgical team and even possibly postpone surgery. [51]

In patients with type 2 diabetes, early discontinuation of GLP-1 analogue therapy before planned surgery is fraught with the risk of hyperglycaemia. [54] Perioperative increases in plasma glucose levels are associated with adverse effects: prolonged hospitalisation, surgical site infection, acute kidney injury, acute coronary syndrome or admission to the Intensive Care Unit. [55, 56] Therefore, preoperative care may be facilitated by additional precautions - drug bypassing consulted with an endocrinologist, collaboration with primary care physicians. Given the increasing use of GLP-1 analogues among patients, the role of prior assessment by the anaesthesiologist or preoperative team is increasing. These measures are intended to help minimise the risk of regurgitation and pulmonary aspiration in perioperative care. [51]

Milder et al. suggest a differentiated approach depending on the reason a patient is taking GLP-1 analogues, and recommend a division between patients with and without type 2 diabetes. They report that in patients with type 2 diabetes, the benefits of taking GLP-1 agonists in the preoperative period may outweigh the risks. In contrast, the opposite may be true in patients taking the drug for weight reduction. These risks may outweigh the benefits. [57] This study is yet another reminder of the importance of an individualized patient approach and personalised interventions.

Ushakumari and Sladen also suggested preoperative ultrasound (ultrasound) examination of the stomach to determine its potential contents. [58] Ultrasound examination is also recommended in patients who have not discontinued a GLP-1 analogue prior to surgery, whereby there is a need to verify gastric filling and assess the risk of regurgitation and pulmonary aspiration. If the stomach is empty, the standard regimen should be followed. If, on the other hand, the stomach is not empty or ultrasound does not allow accurate verification - proceed as with a patient with a "full stomach". [51]

Currently, there is a lack of clear evidence describing the optimum duration of fasting before surgery, so the classic guidelines of 2 or more hours for clear liquids, 6 hours for light meals and 8 or more hours for 'heavy (fried, fatty, meat) meals' are recommended. [59]

Conclusions and perspectives

The rapidly increasing popularity of glucagon-like peptide-1 receptor analogues is not commensurate with the number of new reports on the implications of their use. The topic still requires high-quality research to support anaesthetists in the prevention of gastric content retention and pulmonary aspiration. The limited recommendations are mainly due to the narrow evidence base. This is why future studies of the risk of pulmonary aspiration and clarification of the withdrawal time of GLP-1 analogue drugs are so important. It may also be significant to prove the relationship between the half-life of the substance and the delay in gastric emptying. In addition, from the perspective of anaesthetists, it is important to know the interaction of this group of drugs with others. Due to the phenomenon of gastroparesis, it is worth investigating its relationship with slowed absorption or prolonged action of orally administered substances. Such information would ensure greater safety and efficacy during induction of general anaesthesia and help to clarify perioperative management strategies for patients taking GLP-1 analogues.

In conclusion, the topic of patients taking GLP-1 analogues in perioperative practice requires further exploration. The need to use them with caution and to individualise patient care within the operating theatre deserves to be emphasised. In addition, it is important to have agreement on this topic between specialists in anaesthesiology, endocrinology, gastroenterology and surgery to ensure a holistic approach to the patient and the practical use of recommendations.

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