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Variability in the management of GLP-1 agonists and endoscopic procedures: an opportunity for standardization

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Glucagon-like peptide-1 receptor agonists (GLP-1RAs), also known as incretin mimetics, have significantly revolutionized the treatment of type 2 diabetes *mellitus* (T2DM) and obesity worldwide, far exceeding initial expectations regarding their global prescription (1).

This class of medications has demonstrated weight losses of up to 20 % of baseline body weight (2). Beyond their proven benefits in T2DM and obesity, GLP-1RAs, as well as dual and triple agonists (GLP-1/GIP/glucagon), are being investigated for their effects on conditions such as metabolic-associated steatotic liver disease, various cardiovascular disorders, neurocognitive impairments, and certain addictions. These emerging effects appear to be linked not only to their metabolic action but also to their ability to modulate the chronic inflammatory state underlying these pathologies (3).

Although GLP-1RAs, as well as dual- and triple-action formulations, exhibit an outstanding safety profile, they are not devoid of adverse effects. The most prevalent are gastrointestinal in nature, including nausea, vomiting, constipation, and diarrhea (4). Their ability to delay gastric emptying increases the likelihood of residual gastric content persisting even after a standard fasting period, which could elevate the risk of pulmonary aspiration during procedures performed under deep sedation or general anaesthesia. This has raised growing concerns about their safety. In this regard, isolated cases of pulmonary aspiration have been reported in patients treated with GLP-1RAs during procedures under anesthesia (5,6). Additionally, a recent retrospective study analyzing over 900,000 endoscopic procedures observed a significant increase in the risk of aspiration pneumonia in patients on GLP-1RAs compared to non-users (HR 1.33; 95 % CI, 1.02-1.74). The risk was even higher in combined gastroscopy and colonoscopy procedures (HR 2.26; 95 % CI, 1.23-4.16) and in those using propofol as a sedative agent (HR 1.49; 95 % CI, 1.08-2.06) (7).

As a result of this and other preliminary studies (8,9), the American Society of Anesthesiologists (ASA) recently published a guideline recommending the discontinuation of GLP-1RAs prior to endoscopic or surgical procedures to reduce the risk of aspiration (7 days for weekly formulations and 24 hours for oral formulations) (10). However, while this approach is prudent, it has been considered overly conservative, as it seeks to mitigate a potential aspiration risk that is very low in most patients. Furthermore, this strategy may lead to the postponement or delay of essential diagnostic and therapeutic procedures, potentially compromising patient care.

The ASA recommendations have not received unanimous support from gastroenterologists, primarily due to the lack of evidence supporting the discontinuation of GLP-1RAs before elective endoscopy. A recent retrospective matched case-control study compared the need to repeat upper gastrointestinal endoscopy in non-diabetic patients treated with GLP-1RAs versus those using other weight-loss medications and found no significant differences in procedure repetition (11). Furthermore, it remains unclear whether withholding the medication for a single dose would reliably allow an individual's gastric motility to return to normal. On the

other hand, discontinuing GLP-1RAs complicates the clinical management of diabetes and obesity, negatively affects treatment adherence, and increases the risk of metabolic decompensation. Regarding the risk of aspiration, recent publications have shown that, provided a prolonged liquid-only intake period is observed, there is no significant increase in aspiration risk in patients who continue GLP-1RA treatment (12,13). In another retrospective cohort study, while a small but significant increase in the risk of aspiration pneumonitis was identified in patients on GLP-1RAs undergoing elective upper endoscopy compared to those not on these medications, this did not translate into a higher risk of respiratory failure or ICU admission (14). In this context, the American Gastroenterological Association (AGA) has issued recommendations cautioning against generalizations that could delay procedures without clear justification (15). The AGA suggests that, when feasible, providing patients with a liquid diet the day before sedated procedures may be a more acceptable strategy than discontinuing GLP-1RAs.

The lack of consensus regarding the optimal management of patients treated with GLP-1Ras who require endoscopic procedures is evident. Significant variations exist among different scientific societies in anaesthesiology, endocrinology, and gastroenterology concerning recommendations for discontinuing these medications, the duration of the interruption period, the need to avoid deep sedation or general anaesthesia, the implementation of prolonged fasting and clear liquid intake periods prior to fasting, the use of rapid-sequence intubation, the recognition of signs and symptoms of aspiration risk, and the use of point-of-care ultrasound to assess aspiration risk (16). These inconsistencies highlight the need for prospective studies to analyze not only the risk of aspiration but also the efficacy of different preventive strategies.

The available evidence suggests adopting an individualized approach that balances the risks of residual gastric content with the clinical implications of discontinuing GLP-1Ras (17). A recent consensus document from five prominent North American societies has outlined key recommendations (18), summarized as follows: a) individualize the discontinuation of GLP-1RAs based on the metabolic necessity of the medication and the risk of delayed gastric emptying, which is higher during the dose-escalation phase,

with high doses, weekly formulations, and in the presence of gastrointestinal side effects or conditions that delay gastric emptying, such as Parkinson's disease; and b) implement universal safety measures, such as extending the preoperative liquid diet period to a minimum of 24 hours, using point-of-care gastric ultrasound to assess aspiration risk when feasible, and informing patients about the risks and benefits of potential aspiration, intubation, or procedure cancellation, promoting shared decision-making.

In conclusion, the current evidence remains insufficient to establish definitive clinical guidelines for the optimal management of patients treated with GLP-1RAs undergoing endoscopic procedures under sedation or general anaesthesia. Therefore, efforts should be made to persuade those in charge of gastroenterology and anaesthesiology departments to establish the necessary care pathways to ensure patient safety—not only for those treated with GLP-1RAs—through the development of precise protocols (19). We advocate for an approach that prioritizes the personalization of clinical decisions, aiming to balance the need for essential diagnostic and therapeutic procedures with the preservation of patient safety, considering the specific circumstances of each case. It is imperative for Spanish societies of Gastroenterology and Anaesthesiology to lead efforts in developing standardized protocols to reduce clinical variability in managing these patients. Additionally, these societies should play an active role in generating robust evidence to inform and update clinical guidelines, ultimately enhancing the quality and safety of patient care.

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